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## Neurological Examination ( 19-Oct-2001 )

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Learn to do the neurological examination on a cooperative small breed dog and then you can adapt it to accommodate the size and attitude of other dogs and cats as well as large animals and exotics. When asked how I do a neurological examination on a maniacal aggressive cat or dog my pat answer is: I don't ! However you can make many reliable observations by just observing the animal while it is caged as long as you understand what the normal examination is determining.

#### Why do the neurological examination?

- To determine **if** the nervous system is affected in a disease process.
- To establish as accurate an **anatomic diagnosis** as possible when the nervous system is affected.

Making the anatomic diagnosis should always precede consideration of the differential diagnosis. Despite the tremendous contribution of imaging to neurological diagnosis and one can only guess what innovations lie ahead in the future, the basic hands-on neurological examination is the most valuable cost effective determinant of the clinical diagnosis.

In most cases the anatomic diagnosis is a regional diagnosis and there are essentially 8 regions of the nervous system for consideration.

The **prosencephalon** (forebrain) - includes the two cerebrums and the diencephalon which is the most rostral part of the brain stem and is comprised of the thalamus and hypothalamus. The **pons** and **medulla** are usually considered together as they are the source of the upper motor neuron responsible for the generation of the gait. The **cerebellum** may be the sole anatomic diagnosis or often is considered together with the pons and medulla. This region is sometimes referred to as the caudal fossa which is the space these 3 anatomical areas occupy. The spinal cord is divided into 4 anatomical regions: C1 - C5, C6 - T2, T3 - L3, L4 - Cd.

The peripheral nervous system components are usually considered collectively as the **neuromuscular** system, realizing that there are important sensory systems here as well. Any of these 8 areas can be further divided into smaller components but this serves as a starting point in your anatomic diagnosis.

#### There are 5 components to the neurological examination:

##### 1. Sensorium

The owner is the best observer of any change in the patient's behavior. Significant changes will be obvious but you will often notice subtle changes as you examine the animal. Expressions used to describe these subtle changes include - a vagueness - seems out of touch with reality - is in a world of its own. More acceptable medical terms for the progressive loss of a patient's sensorium are: dullness, lethargy, obtundation, semicoma (stupor) and coma. In my experience the most common site for a focal lesion to cause progressive obtundation or stupor is the diencephalon - presumably from the interruption of the ascending reticular activating system (ARAS) at this level.

##### 2. Gait

The most important aspect of the gait examination is to be able to walk the dog on a non-slippery surface. These are often scarce in most hospitals. If there is no convenient built in carpet in the hospital then purchase a reasonable sized indoor - outdoor carpet that can be rolled out for the exam and rolled out of the way afterwards and can be hosed off in your runs after your patient excretes on it - which is a guarantee. This is just as important for evaluating orthopedic lameness cases. A major objective of the gait evaluation is to determine if a lameness is caused by a neuromuscular disorder or an orthopedic

problem. Lower motor neuron disease can mimic an orthopedic lameness and is often overlooked as the latter problems are so much more common. As you gain experience you will recognize specific gait patterns that suggest the anatomic diagnosis ie., the "two engine" dog with short strides in the thoracic limbs and long delayed strides in the pelvic limbs that has a C6 - T2 disorder.

The following is an attempt to dissect what it is that you are looking for when you evaluate the gait of a patient with a neurological problem. From a neurological perspective, you are assessing the gait for both paresis and ataxia.

**A - Paresis (weakness)** can be defined as a deficiency in the generation of the gait or the ability to support weight. There are two qualities of paresis - upper motor neuron and lower motor neuron.

1 - Lower motor neuron (LMN) paresis is seen as an inability to support weight and the patient walks short-strided - "lame". Other signs include a tendency to collapse, trembling, bunny hopping, and neck flexion. Thoracic limb support requires neurons in the radial nerve to be intact whereas those in the femoral nerve are necessary for pelvic limb support. Lesions that affect specific peripheral nerves to the limbs excluding the radial and femoral nerves will cause abnormal limb postures but still the ability to support weight.

2 - Upper motor neuron (UMN) paresis is seen as a delay in the onset of protraction (the swing phase) and a longer stride with a variable degree of stiffness - spasticity to the stride. Because the UMN tracts and the general proprioceptive (GP) tracts are adjacent to each other at every level of the spinal cord and caudal brain stem lesions at any of these levels usually will cause dysfunction in both systems, therefore, the gait reflects both deficits. GP lesions cause an ataxia in which the patient loses awareness of where its limbs are in space. This also may contribute to the delay in the onset of protraction and be the cause of excessive flexion, adduction or abduction of the limb during protraction and the tendency to bear weight on the dorsal aspect of the paw often referred to as "scuffing or knuckling".

The pattern of gait observed reflects the loss of both of these functional systems and it is not necessary to distinguish between the two systems for your anatomic diagnosis.

Patients that have C1 - 5 lesions and are still ambulatory often have a prolonged stride with the limb kept in extension that appears as if the patient is overreaching its landing site. This is especially evident on turns. Although by strict definition this is a form of hypermetria, I avoid calling it that as there is a strong tendency to relate any hypermetria to a cerebellar disorder which this is not. I refer to this overextension as overreaching or floating. Cerebellar hypermetria has a sudden bursting quality to the onset of protraction and an overflexion of the joints as opposed to the overextension seen here.

**B - Ataxia** is incoordination and comes in three qualities-general proprioceptive, vestibular (special proprioceptive) and cerebellar.

1 - General proprioceptive ataxia represents a loss of awareness of where the limbs are in space and was discussed above with the UMN system which it accompanies.

2 - Vestibular ataxia is a loss of balance reflected in a head tilt, and a tendency to lean, drift, fall or roll to one side. The ataxia is often accompanied by an abnormal nystagmus.

3 - Cerebellar ataxia reflects the inability to modulate the gait generating systems in the brain stem resulting in abnormal "uncontrolled" limb movements that usually are excessively abrupt in onset with an overflexion of the limbs on protraction and abnormal sites of limb placement. These excessive movements are usually referred to as hypermetria. This abnormal gait is usually accompanied by vestibular signs with a loss of balance because there are significant components of the central portions of the vestibular system in the cerebellum.

### **3. Postural Reactions - Muscle Size**

I usually assess these at the same time by standing over the patient with both of us headed in the same direction. In assessing muscle size it is important to try to have the patient bearing the same amount of weight on the two limbs that are being compared. I palpate both thoracic limbs simultaneously from proximal to distal and then flex and extend each for range of motion and as an assessment of muscle tone. When I place the paw back on the floor I place it on its dorsal surface to test for its return to a normal supporting position - the paw placement response. I then move caudally palpating the axial muscles and then palpate and move the pelvic limbs in a manner similar to the thoracic limbs and complete it with the paw placement test. To test the **hopping responses** I then move back to the thoracic limbs and while still standing over - straddling - the patient, I pick up one thoracic limb and hop the patient laterally on the other limb then I shift limbs and hop it back on the first limb. Only hop the dog laterally on the limb. I keep doing this back and forth shifting limbs when the patient reaches the limit of

my stance. I do not move during this procedure and with heavy animals I brace my supporting elbow on my thigh to avoid the strain on my back. The patient does not have to be lifted off the floor for this, only supported so that it is bearing as much weight as possible on the limb being hopped.

To test the hopping responses in the pelvic limbs I stand beside the patient and place my forelimb between the thoracic limbs of the patient so I can lift it up off the floor by its sternum. I then pick up the pelvic limb on the side that I am on and push the dog away from me making it hop on the opposite pelvic limb. I have to change sides to test the other pelvic limb. For heavy animals these hopping responses can be evaluated as you make the patient hemiwalk. I stand beside the patient and pick up both limbs on that side and push the dog away from me. It is important to compare one thoracic limb with the other and one pelvic limb with the other as they are usually faster in the thoracic limbs normally.

These hopping responses essentially test all components involved in voluntary limb movement from sensory receptors in the limb, to ascending spinal cord tracts, to medullary relay proprioceptive nuclei, to thalamic relay nuclei to the thalamocortical pathways, to the internal capsule, to the sensory cortex and the return of the UMN pathways. The latter begin in projection neurons in the adjacent motor cortex, pass into the internal capsule and crus cerebri, to descending UMN pontomedullary systems, into the spinal cord in pyramidal and extrapyramidal UMN tracts, to the ventral grey column LMN, to the muscles in the limb. One might conclude that this is fairly non-specific!! Correct - so why is it so useful? Because first - it tells you if there is an abnormality somewhere in the nervous system and therefore, is a reliable screening test.

Second - its importance in localizing lesions is dependent on what else is abnormal. A patient with a normal gait in the environment of your examination that has hopping deficits on one side most likely has a contralateral prosencephalic lesion. This is a very common relationship and may be the only indication of a prosencephalic lesion. This is one of only 3 tests that you can use in your neurologic examination to determine if a prosencephalic lesion is present and on which side. If you have a patient with a head tilt and a mild loss of balance to one side but otherwise has a normal gait and there is a hopping deficit then if the lesion is focal it is central at the medulla and not in the inner ear. Postural reactions are normal with inner ear - peripheral vestibular system - disorders.

Misleading neurologic description - It is important to be clear and precise with your neurologic descriptions. What does it mean when you read a description in a published case study that describes an 8 year-old Beagle dog as having a right hemiparesis? If the author means that this dog has a normal gait but a right side postural reaction deficit then I would make an anatomic diagnosis of most likely a left prosencephalic lesion. If the author means this dog has a right sided gait deficit with a delay in protraction of the right limbs with spasticity and a tendency to float with the right thoracic limb then my anatomic diagnosis is right C1 - C6. It is important to remember that animals with neuromuscular disorders that still have voluntary movements will hop fast as long as their weight is held up because their proprioception is normal. This observation may help you distinguish between a subtle LMN and UMN paresis.

There are many other postural reactions that can be tested but in my experience the hopping responses are the most reliable and they are all that I routinely perform in this examination.

Many clinicians rely solely on what they call the CP - conscious proprioception response. This is an incorrect term as this tests more than just conscious proprioception. The late Ralph Kitchell published a paper in which he made a point of this common mistake describing that in this test there are somatic afferents that are responding to light touch and pressure in addition to the general proprioceptive neurons. In reality the failure to return the paw to its normal position can be caused by a LMN denervation of the digital extensors, an UMN paresis, or a loss of any of the sensory innervation just described. In addition to this lack of specificity it is my experience that there are some normal patients that when their paw is placed on its dorsal surface they will continue to stand on it until you make them move. This paw placement test should not be relied on in the absence of testing the hopping responses.

Recumbent Animals - It is very important in evaluating these patients to pick them up and hold them in a standing position. Get help if it is a heavy patient. By holding them in this position and lifting them up and down you can determine the quality of muscle tone ie., whether they have a flaccid or spastic paralysis as well as determine if any voluntary movements can be elicited. If there are voluntary movements, while still supporting them you can determine the presence and quality of the hopping response.

#### **4. Spinal Reflexes - Muscle Tone**

Ideally these spinal reflexes and muscle tone will be diminished to absent in LMN disorders and increased in UMN disease. The degree of hypertonia that results from UMN disease will be determined by the amount the lesion interferes with the upper motor neurons that are inhibitory to extensor motor neurons. It is important to evaluate the tone and spinal reflexes together with the gait abnormality. Dogs can exhibit profound neuromuscular paresis with myasthenia gravis and still have normal tone and reflexes. Similarly some dogs with T3 - L3 lesions often have normal muscle tone and reflexes.

For evaluating the spinal reflexes the patient should be placed in lateral recumbency and be as relaxed as possible. The limbs

can be flexed and extended to assess the degree of muscle tone that is present. The only reliable tendon reflex in my experience and the only one that I routinely test is the **patellar reflex**. Holding the stifle in partial flexion the patellar ligament is struck lightly with a hard object. The human pediatric patellar hammer is the best size for our small animals. Both the sensory and motor components of this reflex are contained in the femoral nerves and their components in the L4, 5 and 6 spinal nerves, roots and segments. If you do not get this reflex in either the recumbent limb or non-recumbent limb do not consider it absent until you can not get it in the other position. For some reason that I do not know, this reflex is occasionally absent on either the recumbent or the non recumbent side. You only need to get it once to know it is intact. If the patient will not relax you may not be able to elicit this reflex. It is my experience that the other tendon reflexes are not consistently present in normal dogs and I do not routinely test them.

The **withdrawal (flexor) reflex** is done on both limbs by squeezing a digit with enough pressure to elicit the reflex and a conscious response in a normal patient. Sometimes your digital pressure may be enough. Otherwise use a pair of forceps on the base of the toenail adding enough pressure to get the response or not get it if there is a lesion. Remember that you can have a reflex loss without loss of nociception so you must use care in the amount of pressure you apply to avoid excessive discomfort to the patient and injury by the patient !!

This is a more complex reflex. The sensory neurons tested depend on the digit being tested or the autonomous zone that you select for this stimulus and the motor response involves primarily the sciatic nerve in the pelvic limb (stifle flexion) and its branches, the tibial nerve (digital flexion) and peroneal nerve (tarsal flexion). Beware that the hip flexion that results involves the femoral nerve and most all the ventral branches of the lumbar spinal nerves to the psoas major muscle. An animal with a complete sciatic nerve lesion can flex the hip when the medial aspect of the paw is stimulated (saphenous nerve - sensory branch of the femoral nerve). The segments of spinal cord, roots and spinal nerve ventral branches involved with the sciatic nerve are L6 L7 and S1.

In the thoracic limb there are multiple nerves involved with the withdrawal reflex thus it is a crude test of the entire brachial plexus and cervical intumescence. The sensory nerve or nerves tested depend on the autonomous or cutaneous zones selected. Squeezing the base of the 2nd or 3rd digital nail stimulates the sensory components of the radial nerve dorsally and the median and ulnar nerves on the palmar aspect. The motor neurons involved are in the axillary nerve (shoulder flexion) musculocutaneous nerve (elbow flexion) and median and ulnar nerves (digital flexion). Both the sensory and motor neurons that are involved are associated with the C6 to T2 spinal cord segments - the cervical intumescence.

These flexor responses only require the peripheral nerves and the segments of spinal cord where synapses occur between the afferent and efferent components. A transverse lesion in the spinal cord cranial to these segments that isolates the segments from the rest of the CNS will not cause a loss of these reflexes. They can persist independent of the rest of the CNS.

## **Nociception**

By increasing the amount of pressure on the digit the stimulus becomes a noxious one and in the normal animal will elicit a conscious response. This response is the patient's manifestation of pain. As an anatomist I try to strictly adhere to the approved nomenclature to avoid ambiguity. This is published in the *Nomina Anatomica Veterinaria*. No such Bible exists for medical terminology and is sorely needed. Therefore I appreciate it when I am corrected for an improper use of terminology. In my textbook I refer to this noxious stimulus as the pain stimulus which is incorrect. Once again, my neuroanatomical critic Ralph Kitchell pointed out to me the error of my ways and I applaud him for that. Pain is not a sensory modality. Pain is the subjective response of the patient to a noxious stimulus and varies between individual patients and is dependent on many other factors surrounding the origin of the noxious stimulus. We should all adhere to this terminology! Having clarified that - the conscious perception of the noxious stimulus known as nociception is primarily at the level of the sensory (somesthetic) neocortex in the area of the postcruciate gyrus. To reach this level the entire pathway from the intumescence involved with receiving the noxious stimulus to this sensory cortex must be intact. In general when the afferents that have been stimulated by the noxious event enter the spinal cord dorsal grey column, they synapse on projection neurons there. Most of these will cross to form an ascending pathway in the opposite lateral funiculus but some will form a similar pathway on the same side as the source of the stimulus. In reality there are nociceptive pathways in all funiculi. However there are enough that are contralateral that in a cooperative patient with a prosencephalic lesion involving this pathway or the sensory neocortex there will be a degree of hypalgesia in the limbs on the opposite side. Only a transverse spinal cord lesion cranial to the intumescence involved will produce analgesia. Such a lesion in the cervical spinal cord is usually lethal due to the interruption of UMN respiratory tracts. Recognizing a hypalgesia in the limbs and trunk on one side in a patient with a normal gait is one of the 3 tests used to localize a prosencephalic lesion. It is easier to appreciate in the nasal mucosa which will be described with the cranial nerve part of this examination.

Because there is so much variation between animals in their response to noxious stimuli I do not believe I can reliably recognize the difference between the response to a mild and more severe noxious stimulus - referred to incorrectly as superficial and deep pain. Even if I could, I am not convinced it contributes to my ability to make the anatomic diagnosis. Obviously the presence or absence of nociception with severe transverse thoracolumbar spinal cord lesions is important for

prognosis as well as to specifically locate the site of the transverse lesion. There is one more reflex that I usually test and always test when I am concerned about a possible transverse T3 - L3 lesion in the spinal cord. This is the cutaneous trunci reflex - which I have incorrectly called the panniculus reflex. The sensory neurons stimulated by lightly squeezing or poking the skin over the epaxial muscles of the thoracolumbar vertebrae are contained in the dorsal branches of the spinal nerves innervating the skin at about the level of your stimulus. Synapse occurs in the spinal cord dorsal grey column on long interneurons that then project cranially in the fasciculus proprius. These interneurons terminate on LMN cell bodies in the ventral grey column at C8 and T1 which in turn enter the lateral thoracic nerve that innervates the cutaneous trunci muscle causing the skin to twitch. Rarely this reflex can not be elicited in a normal dog. Starting at the L7 region and stimulating the skin over each successive vertebrae the reflex in most animals does not start to about the midlumbar level but there are many individual variations here. In patients with complete transverse T3 -L3 lesions, this reflex will be absent caudal to the lesion - and more specifically about 2 spinal cord segments caudal to the lesion because of the normal short caudal course of the dorsal branches after they leave the spinal nerve.

This reflex will also be absent with lesions that affect the lateral thoracic nerve or its origin from the C8 and T1 spinal nerves ie., avulsion of the roots of the brachial plexus, nerve sheath neoplasms of these spinal nerves.

The tail should be moved to assess the tone of its muscles and the anal tone should be determined. The **perineal reflex** can be performed by mild digital pressure on the anus or with the blunt end of closed forceps or by squeezing the anal or adjacent perineal skin with forceps and observing contraction of the anal sphincter and tail flexion. The degree of stimulus can be gauged to avoid upsetting the patient when this innervation is still intact. This reflex is dependent on the sacral segments and their spinal nerves and the branches of the pudendal nerves. The tail response is dependent on the caudal segments and nerves. LMN bladder dysfunction is often indirectly assessed by loss of the perineal reflex because of similar involvement of sacral segments and the proximal sacral spinal nerves.

## 5. Cranial Nerves

The cranial nerve exam should be done when the patient is the most relaxed. With very young animals this is often before you handle them at all. In most instances with these young animals - the less restraint the better. For larger patients I prefer to do this cranial nerve exam while standing over the patient as I have been for the postural reactions. For small dogs and all cats I prefer to sit on the floor with my back against the wall - all very comfortable - flex my knees and place the patient with its back lying on my thighs. It is very easy to control the patient this way and especially its head that you are going to examine. Aggressive cats can be rolled in a towel before placing them in this position. The cranial nerve exam can be done "by the numbers" or by region. I much prefer the latter. Either part or all of cranial nerves II thru VIII are evaluated in the region of the eyes.

### Menace - Vision - Pupils

I always start with the menace response and cover one eye as I menace the other. This is a learned response and may not occur until 10 to 12 weeks in puppies and kittens in which case I have to use their ability to follow objects moving in their environment to assess vision. Anatomically this is a II - central visual pathway - VII response. The majority of the central visual pathway is contralateral to the eye being menaced. Some normal animals need a mild stimulus to get a response. I usually tap their orbital region with my hand a couple of times before I do the menace. Then be sure you are not too close with your menacing hand so that you avoid long vibrissae or a sudden air movement that stimulate sensory components of cranial nerve V. If I do not get a response then I immediately touch the eyelids and look for the palpebral response to be sure the facial nerve is functioning. If it is not, then I have to look for eyeball retraction or a head movement as a response to the menace if the patient is visual. Occasionally it is necessary to set up a maze of objects in the animal's environment to see if they can avoid the objects when walking around them.

Immediately following the menace test, the pupil size and response to light should be examined. Some pupil size can be seen in room light - I love cats that have a yellow iris. Most patients have a dark iris which will require some additional light to see the borders of the iris. Hold your pen-light on the midline over the nose to give each eye the same amount of light to look at pupillary size and determine if any anisocoria is present. Then place the light source as close to the eye as possible and if no response occurs move the light around the fundus to be sure all areas are stimulated. After observing this in one eye quickly swing the light into the other eye, observe that eye's response and then swing the light source back to the first eye and keep repeating this. In the normal patient the pupil will constrict rapidly (depending on the species - this is always slow in horses) and as you move the light source from one eye to the other the pupils in both eyes will stay constricted. This is how I observe the indirect or consensual response rather than try to see the response in the opposite eye while I hold the light in the stimulated eye.

When I am teaching, writing examinations or publications I never use the terms direct response (eye stimulated) or indirect - consensual (the other eye) as these terms can be confusing unless you are very careful in your description and in many publications this care is absent. Avoid this confusion by indicating that when the light is directed into OS what happens to the pupil in OS and what happens in OD and do the same for the light directed into OD.

This light reflex is mediated through the rostral brain stem. The retinal ganglion layer neurons involved with this reflex in each optic nerve presumably are directed at the chiasm either into the opposite optic tract (about 75% dog, 65% cat) and the remainder enter the ipsilateral optic tract. These light reflex processes pass over the lateral geniculate nucleus and enter the dorsal thalamus to synapse on neurons in the pretectal nucleus on that side. The majority of these pretectal neurons project thru the caudal commissure to terminate in the oculomotor nucleus on the opposite side of the rostral mesencephalon. Based on this anatomy, light directed into one eye will have a greater influence on the ipsilateral oculomotor nucleus and the response in the stimulated eye may be more rapid and complete than the indirect response in the opposite eye. This is not always obvious in your examination. You would also expect that a lesion limited to one optic tract would cause a decreased response when the contralateral eye was stimulated but this too may be difficult to appreciate.

### **Examples**

If the menace response is absent in one eye with a normal palpebral response and pupils are normal and equal in size and have normal pupillary light reflexes then the lesion causing the unilateral menace deficit is most likely in the contralateral optic tract, lateral ciliary nucleus, thalamocortical fibers, optic radiation part of the internal capsule or visual neocortex primarily in the occipital lobe. This is the central visual pathway for perception. In the dog about 75% of the pathway is contralateral to the eye menaced after the optic chiasm and about 25% remains ipsilateral. Therefore, lesions in this central visual pathway on one side cause a 75% loss of vision in the contralateral eye and 25% loss in the ipsilateral eye but the owners rarely recognize this deficit. The menace test can only determine the contralateral 75% deficit and it is fairly reliable. Even though the contralateral optic tract contains the majority of the pupillary light reflex fibers - assuming that their portion that cross in the optic chiasm is similar to the visual perception pathway - there usually will be no recognizable loss of pupillary light response in the eye tested. This menace test is one of the 3 examinations to determine structural disorders in the prosencephalon.

A patient has no menace response OS with a normal palpebral reflex. There is no anisocoria. Light directed into OS causes no response OU (in both eyes or in each eye). Light directed into OD causes a normal response OU. As you swing the light from OD, where the pupil constricted, back to OS, the OS pupil which was constricted from the OD stimulation is now dilating back to its original size. This asymmetry is repeated as you swing the light back and forth between the two eyes. When you cover OD with your hand, the pupil in OS dilates to its full extent.

#### **Where is the lesion?**

Answer - In OS or the left optic nerve. Most of the time with these lesions there is enough room light entering the normal eye to keep the pupil in the abnormal eye constricted. Occasionally it will be slightly larger than the normal pupil in room light. A patient has normal menace responses. The pupil OD is widely dilated. Light in OD only causes the pupil to constrict in OS. Light in OS only causes the pupil to constrict OS.

#### **Where is the lesion?**

Answer - Right oculomotor nerve - parasympathetic visceral efferent fibers, or ciliary ganglion or its ciliary nerve branches. Be aware of this as the first sign of an extramedullary mass lesion ventral to the diencephalon compressing the oculomotor nerve with loss of the preganglionic parasympathetic function before the somatic efferent neurons to extraocular muscles are affected.

A patient has no menace OD with a normal palpebral reflex. The OD pupil is widely dilated. Light directed into OD causes no response OU. Light directed into OS causes only the OS pupil to constrict.

#### **Where is the lesion?**

Answer - Right optic and oculomotor parasympathetic visceral efferent fibers or the ciliary ganglion or its ciliary nerve branches. A retrobulbar tumor or abscess could do this.

A patient is blind OU - no menace OU - with normal palpebral reflexes. In room light the pupils are mildly dilated. Light directed into OS causes the pupils to constrict OU. Light directed into OD causes the pupils to constrict OU.

#### **Where is the lesion?**

Answer - **Both** eyeballs, optic nerves optic chiasm or optic tracts. The two most common disorders that cause these specific signs are a retinal degeneration (SARDS-sudden acquired retinal degeneration) and optic neuritis.

From my clinical experience it appears that animals with lesions in the sites just described can lose their visual perception and be clinically blind but still have light responsive pupils when a bright light is directed into the eyes. However, in room light there is insufficient light to permit normal constriction. This may reflect that the disease processes involved tend to spare the pupillary light reflex neurons in cranial nerve II or more likely to lose the light reflex completely it is necessary to interfere with the function of all of these neurons whereas vision is lost after a certain threshold percentage of retinal ganglion layer neurons are dysfunctional. In other words the pupillary light reflex neurons are the last to go when lesions disrupt the retina or optic nerve.

Anisocoria can result from many intraocular disorders. Iris atrophy is fairly common in older animals and creates dilated

unresponsive pupils with no interference with vision. Neurological causes of anisocoria include disturbances to cranial nerves II, III and the sympathetic ocular innervation.

Complete sympathetic paralysis of the head (Horner's syndrome) causes a miosis, smaller palpebral fissure and a protuded third eyelid. Facial hyperthermia and decreased nasal air flow on the affected side are very difficult to appreciate in small animals. This sympathetic paralysis most commonly involves some component of the pre or postganglionic sympathetic LMN. In very acute severe C1 - C8 spinal cord lesions an UMN Horner's syndrome may occur. This is most commonly seen in hemiplegic dogs associated with ischemia or infarction caused by fibrocartilaginous emboli. A persistently miotic pupil in a small animal with the signs of an avulsion of the components of the brachial plexus localizes the injury to the level of the roots or spinal nerves at the vertebral column.

It is important to remember that in general the size of the pupils represents a balance between the amount of light entering the eye and stimulating the oculomotor neurons that innervate the iris constrictor muscle and the emotional state of the patient which influences the sympathetic innervation of the iris dilator muscle.

### **Strabismus**

While examining the eyes you can appreciate whether they are normally positioned in the orbits. Abnormal eye positions reflect a lack of innervation of the extraocular muscles or a disorder with the vestibular system. The latter is most common and the vestibular strabismus only occurs in some positions of the head. Somatic efferent neurons in the oculomotor nerve prevent a lateral and slightly ventral strabismus. The abducent neurons prevent a medial strabismus. The trochlear neurons prevent an excessive extorsion of the eye which can only be seen in the cat with the lateral positioning of the dorsal aspect of its vertical pupil. In the dog you would have to do a fundic exam and look at the position of the normally vertical superior vein at the optic disc. A quick assessment of the function of the oculomotor nerve innervation to the medial rectus muscle and the abducent nerve innervation to the lateral rectus is to test for normal physiologic nystagmus by moving the head side to side. As you move the head to the right both eyes will move abruptly - jerk in that direction, which tests the abducent nerve in the right eye and the oculomotor nerve in the left eye as both eyes will jerk together. On moving the head back to the left the opposite nerves will be tested. The stimulus for this response is the movement of fluid in the semicircular ducts and stimulation of vestibular nerve (VIII) receptors in the inner ear. These impulses will be projected thru the vestibular nuclei into the medial longitudinal fasciculus in the brain stem which projects to the somatic efferent neurons of the oculomotor and abducent nerves. This normal response can be readily elicited in most dogs but in some cats the eye movements will only occur at the end of the head excursion. This takes a long time to write and just a few seconds to do.

### **Nystagmus**

As I stand over the dog's head, following the menace and pupil examination, I look for any strabismus or any abnormal resting - spontaneous nystagmus. I then move the head side to side to see if the eye movements are normal and then hold the head still in one lateral position and see if any abnormal positional nystagmus develops - then move the head to the opposite side and hold it still and look for abnormal nystagmus in that position and then I extend the head and neck and hold it still and look for abnormal nystagmus. In dogs and cats when the head and neck are extended, the eyes normally elevate to stay in the center of the palpebral fissure. With vestibular system disorders the eye on the affected side usually fails to elevate completely giving you a vestibular strabismus. When the head is held still there should be no nystagmus. Nystagmus is normal whenever the head is moved. In a severe vestibular system disorder a nystagmus occurs continuously regardless of the position of the head. This is an abnormal nystagmus referred to as a resting or spontaneous nystagmus. In less severe vestibular system disturbances an abnormal nystagmus may only occur when the head is held in various positions as just described. This is referred to as an abnormal positional nystagmus. Occasionally in very mild cases it will only show up when the patient is placed in dorsal recumbency with the head and neck extended. The direction of the nystagmus is defined as the direction of the fast phase of the eye movements. The one rule that can be relied on is that when the vestibular disturbance involves the inner ear receptors or the vestibular part of the vestibulocochlear nerve (VIII), the direction of the jerk nystagmus is always opposite to the side of the lesion. The latter is the direction of the head tilt and loss of balance.

### **Facial and Trigeminal Neurons**

Although portions of these cranial nerves have already been assessed, I routinely reconsider them now. I gently touch the eyelids with a pair of forceps coming at the eyes from caudally so the forceps will not be seen. There is considerable overlap of the eyelid innervation by the trigeminal nerve ophthalmic branches medially and the maxillary branches laterally therefore I make no attempt to distinguish between the two. The sensory nerves stimulated are branches of the trigeminal nerve (CN V) and the motor response is via branches of the facial nerve (CN VII). Connections between the two involve the pons and medulla. For other areas of facial nerve innervation I look for normal flaring of the nostrils on inspiration, hold the head and neck in extension and look at the corners of the lips for evidence of mucosa showing on the parietic side and abnormal drooling on that side. I also assess the ability to move the ears in those patients with erect ears but do not spend much time on

flop-eared dogs to avoid frustration. Sometimes a normal ear will move when you blow air into it. There is no need for the examiner to get excessively stressed in this process. Remember that dogs and cats with facial paralysis will not have a smaller palpebral fissure (ptosis) unlike the herbivores nor will their nose deviate to the normal side. When you see the nose deviated to one side in a dog this usually is a reflection of excessive contraction of the facial muscles on that side referred to as hemifacial spasm but it is not spasmodic-episodic as it is described in humans. It is a continual deviation. This is most commonly associated with a presumed irritation of the facial nerve from an otitis media. These dogs will have a narrowed palpebral fissure and an ear pulled dorsally and medially on that side. On testing the palpebral reflex there may be slight movement of the eyelids. This has been described as a denervation contracture of the facial muscles but these muscles will often relax during local or general anesthesia which refutes that consideration at least for most cases. This rarely occurs in the cat.

To complete my evaluation of the trigeminal nerve I palpate the muscles of mastication. The only evidence of a unilateral motor trigeminal nerve deficit will be the denervation atrophy that can be palpated. They can still bite!! You need bilateral loss of this mandibular nerve innervation to get a loss of the ability to use the jaw. When this occurs the lower jaw will be dropped so the mouth is continually open and can not be closed. The most common cause of a sudden onset of a dropped lower jaw is an immune-mediated trigeminal neuritis. The most common cause of unilateral atrophy of these muscles is a nerve sheath neoplasm in the dog and more likely lymphoma in the cat. Bilateral atrophy of the muscles of mastication is often seen in older dogs with no evidence of any dysfunction. One cause may be a chronic myositis. Occasionally this atrophy and accompanying fibrosis is severe enough to prevent the jaw from opening.

On a routine examination I always touch the nasal septum with the end of my closed forceps as a test of both the sensory innervation by the trigeminal nerve - specifically ophthalmic branches via the ethmoidal nerve, but also as a very sensitive test for nociception and therefore this projection pathway which involves the contralateral prosencephalon. This is one of the three tests that I have described that will evaluate prosencephalic function. With prosencephalic lesions this nasal septum will never be analgesic just hypalgesic because some of the nociceptive pathway stays ipsilateral and the incomplete crossing occurs in the pons and medulla.

When you determine that there is nasal hypalgesia the lesion responsible for this can either be in the ipsilateral trigeminal nerve or in the contralateral prosencephalon. You differentiate between the two locations based on the rest of the clinical signs that are present. Are they related to the caudal brain stem and therefore this is a trigeminal nerve problem or are they prosencephalic and that is the basis for the hypalgesia?

## IX - X - XII

These 3 cranial nerves are examined together with the so-called "gag reflex". This is done rapidly as the patient usually objects to the manipulation that is necessary and especially cats. You grasp the upper jaw with one hand and pull down on the lower jaw with the other hand opening the mouth. This effort will test the tone - resistance in the muscles of mastication (CN V). You quickly look at the size of the tongue for atrophy - hypoglossal nerve (CN XII) and push the tongue with your finger to see if it moves. Then insert your finger deep into the oropharynx to assess the tone and sensory perception that you will stimulate. These latter functions are dependent on the innervation by the pharyngeal branches of the glossopharyngeal (IX) and vagal (X) nerves. This assessment of the gag response is difficult to evaluate and is usually very subjective. A more reliable indication of dysphagia usually comes in the form of a complaint by the owner as they watch their pet try to eat and swallow.

The following is an outline of the order of the cranial nerve exam just described:

- |                               |  |
|-------------------------------|--|
| - Menace Response             | II - central visual pathway to occipital lobe<br>VII = closure of palpebral fissure                            |
| - Pupil Size - Light Response | II - brain stem<br>III parasympathetic-ciliary ganglion - nerves = pupil constriction direct and indirect      |
| - Eye Position                | Strabismus - III = ventrolateral<br>Strabismus - VI = medial   |
| - Eye Movements               | Normal vestibulo-ocular nystagmus<br>VIII - brain stem - III = adduction<br>VIII - brain stem - VI = abduction |
| - VIII - Vestibular           | Strabismus in some eye positions<br>Abnormal nystagmus (head not moving)                                       |
| - Facial Muscles              | VII - position, tone, movement: eyelids, ears, lips, nose  |



- Menace Response	II - VII
- Palpebral Reflex	V - VII
- Facial Sensation	V
- Palpebral Reflex	V - VII - cutaneous, autonomus zones
- Nociception	Nasal mucosa - Ophthalmic branch V
- Masticatory muscles	V - Mandibular branch V Muscle size, tone-jaw closure
- Gag Reflex	Jaw tone - V
- Tongue Size Movement	XII
- Reflex Gagging, Swallowing	IX, X

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## Neurological Syndromes (7-Feb-2003)

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The nervous system, unlike other body systems, is comprised of myriad subparts that typically have unique neuroanatomical and neurophysiological functions. Accordingly, localizing lesions within different areas of the nervous system can be quite a challenge. This task is made easier by utilizing the neurological syndrome approach. A "syndrome" is defined as a group of clinical signs that are usually seen together and are representative of specific organ system involvement. The syndrome concept has special importance in the nervous system, since specific lesions within the central nervous system, peripheral nervous system, and skeletal muscle result in predictable, specific clinical signs. Therefore, through the recognition of certain key clinical signs (i.e., a syndrome) a lesion can be localized within any of these areas. This concept of neurological syndromes provides the basis for lesion localization, without which differential diagnosis of disease cannot logically be pursued [1-3]. Note that in localizing a lesion, it is not necessary that all the clinical signs listed for each syndrome be observed: a sufficient number of key clinical signs are usually present to permit accurate identification of the syndrome. Diseases commonly seen with each syndrome are listed and designated as more likely to be seen in dogs (D), cats (C), or in both species (D + C).

The following syndromes will be discussed:

- Lumbosacral Syndrome
- Thoracolumbar Syndrome
- Cervicothoracic Syndrome
- Cervical Syndrome
- Pontomedullary Syndrome
- Cerebellar Syndrome
- Vestibular Syndrome
- Midbrain Syndrome
- Diencephalic Syndrome
- Cerebral Syndrome
- Multifocal Syndrome
- Paroxysmal Syndrome
- Myopathic Syndrome
- Neuropathic Syndrome

### **Lumbosacral Syndrome**

Lesions involving spinal cord segments L4 - 5 through S1 - 3 (+ coccygeal segments) or lumbosacral nerve roots that form the cauda equina (including femoral, obturator, sciatic, pudendal, pelvic, and coccygeal nerves) will result in a lumbosacral syndrome. The lumbosacral syndrome reflects various degrees of involvement of the pelvic limbs, bladder, anal sphincter, and tail. Clinical signs will range from flaccid weakness to paralysis of pelvic limbs and tail. Patellar and withdrawal reflexes (as well as gastrocnemius and cranial tibial reflexes) may be depressed or absent in pelvic limbs, as may be perineal (anal) and bulbocavernosus (in male dogs) reflexes. Tone in pelvic limb muscles may be reduced or absent. After 1 to 2 weeks of clinical signs, segmental muscle atrophy due to denervation will be observed. "Segmental" refers to the particular spinal cord segment involved in the lesion (e.g., segmental atrophy may develop in the iliopsoas, quadriceps, and sartorius muscles following an injury to the L4 - 6 spinal cord segments). Pain perception in pelvic limbs, tail, and perineum may be reduced or absent. Pelvic limb postural reactions such as hopping and placing may be depressed. Thoracic limb function is unaffected. Normal micturition requires synchronized contraction of the urethral smooth muscle and relaxation of the urethral skeletal

muscle. Urethral smooth muscle is supplied by pelvic (parasympathetic) and hypogastric (sympathetic) nerves; pelvic and hypogastric nerves form the pelvic plexus. The pudendal nerve innervates the urethral skeletal muscle. Lesions involving the pelvic nerves, sacral cord segments, or pathways to and from the brainstem will abolish the micturition reflex. Consequently, the bladder will distend with urine and eventually overflow. Lesions of the sacral segments will also result in loss of innervation to the skeletal muscle of the urethra. As a result of minimal urethral resistance, manual expression of the bladder is easy in such cases. Thus, animals with sacral cord lesions may suffer from continual overflow incontinence. The anal sphincter may be flaccid and dilated, resulting in fecal incontinence. Since the external anal sphincter is innervated by the pudendal nerve, which also originates in the sacral segments, the perineal (anal) reflex provides a good assessment of sacral spinal cord function. In some animals with lumbosacral disk extrusion, one pelvic limb may be held in partial flexion or a repetitive "stamping" motion may be observed. These animals frequently show considerable pain on manipulation of the limb and lumbosacral spine. This combination of signs is termed "root signature" and is believed to be associated with nerve root compression or entrapment by a fragment of extruded disk material. Note that some animals with the lumbosacral syndrome may be paretic or paralyzed in the pelvic limbs, with reduced reflexes and muscle tone, but have normal anal sphincter function. In other animals, anal sphincter and bladder dysfunction may be the principal clinical signs, with only mild pelvic limb weakness. Both groups of animals have a lumbosacral syndrome, but the lesion occurs at slightly different levels of the lumbosacral spinal cord or lumbosacral nerve roots. The principal clinical signs of the lumbosacral syndrome are listed in Table 1, and the diseases known to produce this syndrome are outlined in Table 2.

Table 1. Principal Signs of the Lumbosacral Syndrome	
	<ul style="list-style-type: none"> <li>• Weakness/paralysis of pelvic limbs and tail</li> <li>• Depressed pelvic limb reflexes and flaccid muscle tone</li> <li>• Muscle atrophy in pelvic limbs, and/or hip muscles</li> <li>• Postural reaction deficits in pelvic limbs</li> <li>• Dilated anal sphincter</li> <li>• Depressed bulbocavernosus reflex</li> <li>• Reduced sensitivity (hypesthesia) in perineal area, pelvic limbs, or tail</li> <li>• Urinary incontinence</li> <li>• Fecal incontinence</li> <li>• Root signature</li> </ul>

Modified from: Braund KG. An approach to diagnosing neurological disease. Waltham Focus 1999; 9:23-30 [2].

Table 2. Diseases Associated with the Lumbosacral Syndrome	
Degenerative Disorders	None
Degenerative Structural and Compressive Disorders	Lumbosacral stenosis; disk disease; spondylosis deformans; dural ossification; nervous system degeneration in Ibizan Hounds; spinal synovial cysts
Developmental Disorders	Spina bifida; sacrocaudal dysgenesis; dermoid sinus; myelodysplasia; transitional vertebrae
Endogenous Metabolic Disorders	None
Inflammatory Disorders	Rabies; granulomatous meningoencephalomyelitis; mycotic diseases; parasitic encephalomyelitis; abscessation
Neoplasia	Spinal cord tumors; peripheral nerve tumors
Neurotoxic Disorders	None
Neurovascular Disorders	Infarction; fibrocartilaginous embolization; hemorrhage; hemorrhagic myelomalacia; traumatic feline ischemic myelopathy
Nutritional Disorders	None
Storage Disorders	None
Traumatic Disorders	Spinal trauma

Modified from: Braund KG. Clinical Syndromes in Veterinary Neurology. St Louis: Mosby, 1994 [1].

#### Notes -

- a) In canine neural angiostrongylosis caused by *Angiostrongylus cantonensis*, neurological signs are commonly seen in puppies from 5 to 16 weeks of age and are characterized by a lumbosacral syndrome (See parasitic encephalomyelitis).
- b) Several conditions such as transitional vertebrae, dural ossification, and spondylosis deformans may be detected by radiography/imaging but are usually subclinical.
- c) Spinal trauma in the lumbosacral region is usually associated with pelvic or sacrocaudal fractures.
- d) Inflammatory disorders affecting the lumbosacral region are not commonly reported. Multiple granulomas with fungal elements have been observed in the lumbosacral subarachnoid space with compression of the cauda equina.
- e) Signs of a lumbosacral syndrome may result from certain polyneuropathies, such as cauda equina polyradiculoneuritis (See neuropathic disorders) and motor neuron diseases
- f) In nervous system degeneration in Ibizan Hounds, patellar reflexes are absent, but without evidence of muscle atrophy.
- g) In cats with nemaline myopathy, patellar reflexes are also depressed/absent and there may be gluteal muscle atrophy.
- h) Common causes of the lumbosacral syndrome seen in practice
  - Pelvic fractures and luxations (D + C)
  - Lumbar stenosis (D)
  - Fibrocartilaginous embolization (D)
  - Sacrococcygeal dysgenesis (C)

### **Thoracolumbar Syndrome**

A spinal cord lesion located between cervical and lumbar enlargements (intumescences), i.e., between T3 and L3 cord segments, will produce a thoracolumbar syndrome, which is commonly encountered in dogs and cats. The thoracolumbar syndrome is characterized by spastic weakness or paralysis of pelvic limbs (spasticity is associated with increased muscle tone, especially in extensor muscles). Ataxia may be observed in ambulatory animals (e.g., crossing of the pelvic limbs when walking, knuckling, or abnormal abduction or protraction of the pelvic limbs). Pelvic limb reflexes are intact (normal or increased); however, postural reactions such as hopping and placing are depressed in pelvic limbs. In some animals, reflex testing may induce *clonus* - spasms in which contraction and relaxation of limb muscles alternate in rapid succession. Flexor reflex testing may also induce prolonged, repetitive flexion of the limb being tested in the absence of repeated stimuli [4]. A crossed extensor reflex may be observed. Thoracic limb function is normal. Animals with thoracolumbar disk disease may keep their backs slightly arched ("kyphosis"). The cutaneous trunci reflex can be a valuable test for localizing a focal lesion in the thoracolumbar spinal cord as reflex contraction of the subcutaneous musculature will be reduced or absent caudal to the level of the lesion, but exaggerated at the level of, or immediately above, the area of cord involvement. Similarly, there is reduced cutaneous sensation along the dorsal spine behind the lesion site, but sensation is increased at, or immediately above the level of the lesion. In dogs with thoracolumbar disk disease, digital pressure on the spine at the level of disk extrusion will usually elicit back pain. Spinal cord lesions rostral to the sacral segments can result in increased tone (spasticity) in the skeletal muscle of the external urethral sphincter, making the bladder very difficult to express manually, so that catheterization or pharmacologic intervention is usually required. Consequently, bladder distension and occasional overflow incontinence are usually present. A reflex bladder with detrusor asynergia may develop after a few weeks and an incontinence is often characterized by sporadic spurting of urine.

Segmental muscle atrophy is not a feature of the thoracolumbar syndrome; however, atrophy caused by disuse can occur in animals with long-term or permanent paralysis. Such atrophy is usually generalized and involves all muscles of the spine caudal to the level of the spinal cord lesion, as well as muscles of the pelvic limbs.

An acute, compressive lesion of the thoracolumbar spinal cord occasionally may be accompanied by a Schiff-Sherrington posture, which is observed as rigid extension of the thoracic limbs with the animal in lateral recumbency. However, voluntary movement (with support) and postural reactions, such as wheelbarrowing and hopping, are normal in the thoracic limbs. The wheelbarrow reaction is particularly useful for testing thoracic limb function: it is usually depressed in animals with cervicothoracic or cervical syndromes. It should be noted that this test is manipulative and should not be performed on animals with vertebral column injuries. The principal clinical signs of the thoracolumbar syndrome are listed in Table 3, and the diseases known to produce this syndrome are outlined in Table 4.

#### Notes -

- a) Several conditions such as hemivertebra, dural ossification, spondylosis deformans, and stenosis of the vertebral canal (e.g., in the thoracic region) may be detected by radiography/imaging but are usually subclinical. Similarly, spina bifida may be subclinical.
- b) Spinal trauma in the thoracolumbar region is frequently associated with thoracolumbar fractures or luxations/subluxations. In animals (especially cats) with Nutritional secondary hyperparathyroidism, neurological signs of a thoracolumbar syndrome most often relate to spinal fractures associated with severe vertebral osteopenia.

- c) Epidural migration of parasites, e.g., adult heartworms (*Dirofilaria immitis*) is occasionally seen in dogs producing a thoracolumbar syndrome.
- d) A degenerative myelopathy associated with malignant tumors located outside of the nervous system may occasionally result in a thoracolumbar syndrome (see paraneoplastic myelopathy)
- e) Common causes of the thoracolumbar syndrome seen in practice
- Intervertebral disk disease(D)
  - Spinal fractures (D + C)
  - Degenerative myelopathy (D)
  - Diskospondylitis (D)
  - Metastatic lymphosarcoma (C)

Table 3. Principal Signs of the Thoracolumbar Syndrome
<ul style="list-style-type: none"> <li>• Weakness or paralysis of pelvic limbs</li> <li>• Pelvic limb reflexes normal or brisk (may seen clonus)</li> <li>• No muscle atrophy in pelvic limbs</li> <li>• Postural reaction deficits in pelvic limbs</li> <li>• Reduced/absent cutaneous trunci reflex behind level of lesion</li> <li>• Increased local sensitivity (hyperesthesia) at level of lesion</li> <li>• Reduced sensitivity (hypesthesia) behind level of lesion</li> <li>• Urinary incontinence</li> <li>• Thoracolumbar kyphosis</li> <li>• ± Schiff-Sherrington posture</li> </ul>

Modified from Braund KG: An approach to diagnosing neurological disease. Waltham Focus 1999; 9:23-30 [2].

Table 4. Diseases Associated with the Thoracolumbar Syndrome	
Degenerative Disorders	Afghan Hound myelopathy; degenerative myelopathy; encephalomyelopathy in young cats; Hound ataxia; Kooiker Dog myelopathy; Labrador Retriever axonopathy; nervous system degeneration in Ibizan Hounds
Degenerative Structural and Compressive Disorders	Calcinosis circumscripta/tumoral calcinosis; disk disease; dural ossification; osteochondromatosis; spinal synovial cysts; spondylosis deformans
Developmental Disorders	Arachnoid cysts; dermoid sinus; hemivertebra; myelodysplasia; spina bifida; stenosis of the vertebral canal; syringomyelia and hydromyelia
Endogenous Metabolic Disorders	None
Inflammatory Disorders	Distemper; feline infectious peritonitis; feline leukemia virus; granulomatous meningoencephalomyelitis; mycotic diseases; parasitic encephalomyelitis; protothecosis; rabies; toxoplasmosis and neosporosis
Neoplasia	Spinal cord tumors; paraneoplastic myelopathy
Neurotoxic Disorders	None
Neurovascular Disorders	Infarction; fibrocartilaginous embolization; hemorrhage; hemorrhagic myelomalacia
Nutritional Disorders	Nutritional secondary hyperparathyroidism
Storage Disorders	Globoid leukodystrophy; mucopolysaccharidosis type VI
Traumatic Disorders	Spinal trauma

Modified from: Braund KG. Clinical Syndromes in Veterinary Neurology. St Louis: Mosby, 1994 [1].

### Cervicothoracic Syndrome

The cervicothoracic spinal cord segments that extend from C6 through T2 form an enlarged area of the cord known as the cervical intumescence. The gray matter of these segments gives rise to various nerves (e.g., suprascapular, musculocutaneous,

axillary, radial, median, and ulnar nerves) supplying thoracic limb muscles. A lesion in this region of the spinal cord produces signs of a cervicothoracic syndrome. The hallmarks of the cervicothoracic syndrome are weakness or paralysis in both thoracic limbs, in all four limbs (i.e., tetraparesis or tetraplegia), in limbs on the same side of the body (i.e., hemiparesis or hemiplegia), or in only one thoracic limb (i.e., monoparesis or monoplegia). Ataxia may be observed in ambulatory animals. Other signs include depressed or absent reflexes (tricipital, bicipital, withdrawal) and decreased or flaccid muscle tone in one or both thoracic limb(s). As with a lumbosacral syndrome, segmental muscle atrophy due to denervation is usually observed in the thoracic limb(s) of animals 1 - 2 weeks after spinal injury. In pelvic limbs, reflexes are intact and may be increased (brisk), but there is no atrophy. Postural reactions, such as hopping and placing, may be depressed in all limbs, especially in the thoracic. In some instances, animals will clumsily propel themselves on their chins using their pelvic limbs, with thoracic limbs drawn to their flanks. The cutaneous trunci reflex, mediated by the lateral thoracic nerve which originates in cord segments C8 - T2, may be depressed or absent unilaterally or bilaterally, depending on the extent and location of the lesion. In animals with unilateral loss, there may still be a twitch on the contralateral trunk (called the consensual response, which is caused by fibers crossing within the spinal cord) and this can sometimes be mistaken for an ipsilateral twitch. Urinary incontinence (similar to that seen with the thoracolumbar syndrome) is usually observed. Animals with lesions in cord segments T1 - T3 may have signs of a Horner's syndrome - miosis (small pupil), ptosis (upper lid droop), enophthalmos (sunken globe) and prolapse of the third eyelid. A cervicothoracic syndrome may occur in animals (usually dogs) with hydrosyringomyelia (See Syringomyelia and Hydromyelia), often in association with Chiari malformations. With continuing expansion of the hydrosyringomyelia, ventral horn cells may become involved leading to neurogenic muscle atrophy and weakness, while dorsal expansion of the lesion may impact the dorsal horn and decussating spinothalamic tracts leading to segmental sensory loss and/or paraesthesia over shoulder and neck dermatomes (leading to persistent scratching at the flank or shoulder/neck area). This group of signs has been termed a "central cord syndrome". The central cord syndrome may also occur with intramedullary spinal cord tumors (See Intramedullary Tumors). The principal clinical signs of the cervicothoracic syndrome are listed in Table 5, and the diseases known to produce this syndrome are outlined in Table 6.

Table 5. Principal Signs of the Cervicothoracic Syndrome
<ul style="list-style-type: none"> <li>• Weakness/paralysis in: <ul style="list-style-type: none"> <li>- all four limbs (i.e., tetraparesis/tetraplegia),</li> <li>- limbs on the same side of the body (i.e., hemiparesis/hemiplegia),</li> <li>- only one thoracic limb (i.e., monoparesis/monoplegia)</li> </ul> </li> <li>• Depressed reflexes and flaccid muscle tone in thoracic limb(s), muscle atrophy after 1 - 2 weeks</li> <li>• Normal/increased reflexes and muscle tone, without muscle atrophy, in pelvic limb(s)</li> <li>• Postural reaction deficits in one thoracic limb, in limbs on the same side, or in all limbs</li> <li>• Increased local sensitivity (hyperesthesia) at level of lesion</li> <li>• Reduced sensitivity (hypesthesia) behind level of lesion</li> <li>• Persistent scratching at one side of the shoulder/neck region</li> <li>• Cutaneous trunci reflex depressed or absent (unilaterally or bilaterally)</li> <li>• Horner's syndrome <ul style="list-style-type: none"> <li>- Miosis (may be the only signs of Horner's syndrome)</li> <li>- Enophthalmos</li> <li>- Ptosis</li> <li>- Protrusion of third eyelid</li> </ul> </li> </ul>

Modified from Braund KG: An approach to diagnosing neurological disease. Waltham Focus 1999; 9:23-30 [2].

#### Notes -

- a) One condition that mimics a unilateral cervicothoracic syndrome is traumatic avulsion of the brachial plexus (see brachial plexus avulsion). Animals with this disorder may show evidence of areflexia, muscle atrophy, and weakness/paralysis (i.e., monoparesis/monoplegia) of one thoracic limb, together with signs of a partial Horner's syndrome in which only miosis is observed. The miosis will be ipsilateral, i.e., on the same side as the paralyzed thoracic limb. In animals with brachial plexus avulsion, postural reactions will be depressed in the affected limb but normal in all other limbs.
- b) Another neuropathic condition that mimics a cervicothoracic syndrome is brachial plexus neuropathy (See Neuropathies).
- c) Spinal trauma in the cervicothoracic region may be associated with cervicothoracic fractures or luxations/subluxations.
- d) Brachial plexus sheath tumors often extend into the vertebral canal and produce spinal cord compression and signs of a

cervicothoracic syndrome (See Intradural-extramedullary Tumors).

e) Subclinical spina bifida has been found involving C7 vertebra in some puppies with Labrador Retriever axonopathy.

f) Common causes of the cervicothoracic syndrome seen in practice:

- Brachial plexus avulsion (D)
- Brachial plexus sheath tumors (e.g., neurofibroma) (D + C)
- Fibrocartilaginous embolization (D)
- Cervical spondylomyelopathy (D)
- Disk disease (D)

Table 6. Diseases Associated with the Cervicothoracic Syndrome	
Degenerative Disorders	Afghan Hound myelopathy; motor neuron disease in German Shepherds; hereditary polioencephalomyelopathy of the Australian cattle dog
Degenerative Structural and Compressive Disorders	Calcinosis circumscripta/tumoral calcinosis; cervical spondylomyelopathy; disk disease; dural ossification; osteochondromatosis; spinal synovial cysts
Developmental Disorders	Arachnoid cysts; dermoid sinus; syringomyelia and hydromyelia; spina bifida
Endogenous Metabolic Disorders	None
Inflammatory Disorders	Distemper; feline leukemia virus; granulomatous meningoencephalomyelitis; mycotic diseases; parasitic encephalomyelitis; rabies; toxoplasmosis and neosporosis
Neoplasia	Spinal cord tumors
Neurotoxic Disorders	None
Neurovascular Disorders	Infarction; fibrocartilaginous embolization; hemorrhage; hemorrhagic myelomalacia
Nutritional Disorders	Hypervitaminosis A
Storage Disorders	Globoid leukodystrophy
Traumatic Disorders	Spinal trauma; brachial plexus avulsion

Modified from: Braund KG. Clinical Syndromes in Veterinary Neurology. St Louis: Mosby, 1994 [1].

### Cervical Syndrome

A lesion between C1 and C5 spinal cord segments produces the cervical syndrome. As with the thoracolumbar syndrome, clinical signs reflect disruption of white matter pathways rather than gray matter involvement (as seen in lumbosacral and cervicothoracic syndromes). With a cervical syndrome, clinical signs may range from weakness to spastic paralysis of all four limbs (i.e., tetraparesis or tetraplegia) or of limbs on the same side of the body (i.e., hemiparesis or hemiplegia). Ataxia may be observed in ambulatory animals. Postural reactions are usually depressed or absent in all limbs, and urinary incontinence, similar to that seen in the thoracolumbar syndrome, may be evident. Dorsal and lateral compressive lesions of the cervical spinal cord may result in signs being more severe in the pelvic limbs (perhaps because of the more superficial location of the ascending proprioceptive pathways from the pelvic limbs), while a ventral median compressive lesion may produce more severe signs in the thoracic limbs (perhaps because of the more medial location of descending motor tracts projecting to the cervical intumescence [5]. A more centrally located lesion within the spinal cord (e.g., a centrally expanding intramedullary tumor or central necrosis secondary to acute spinal trauma) may produce more severe signs in the thoracic limbs because motor tracts of the thoracic limbs lie more centrally than do those of the pelvic limbs [6]. Reflexes and muscle tone are intact or increased in all limbs. In some animals with a severe cervical cord lesion, muscle tone may be increased to the point of pronounced extensor rigidity that may be clasp-knife in character (in which a rigidly hyperextended limb suddenly gives way to forced flexion). There is no evidence of segmental muscle atrophy in any of the limbs. Affected animals may experience variable loss of pain perception in all limbs and in the neck caudal to the level of the lesion; however, it is unusual to detect complete loss of pain sensation, since spinal cord injury of such magnitude would most likely be accompanied by respiratory failure. Cervical muscle spasms, pain on palpation or manipulation, and cervical rigidity due to splinting of the neck muscles will be present in some animals, e.g., dogs with cervical disk disease. These dogs strenuously resist flexion and extension of their necks and they may assume an abnormal posture with the nose held close to the ground and the back arched. In some dogs with cervical disk disease, one thoracic limb may be held in partial flexion, or a repetitive "stamping" motion may be observed. These animals frequently show considerable pain on manipulation of the limb and neck. This combination of signs is termed "root signature" and is believed to be associated with nerve root compression or entrapment by a fragment of

extruded disk material.

Occasionally, an animal may manifest a variable degree of respiratory difficulty. Rarely, an ipsilateral Horner's syndrome may be present in an animal with a severe destructive lesion in the cervical cord, e.g., infarction secondary to fibrocartilaginous embolization.

The central cord syndrome mentioned in the cervicothoracic syndrome may also occur in the cervical region in conjunction with hydrosyringomyelia or an intramedullary tumor. In affected animals, segmental sensory loss and/or paresthesia, along with lower motor neuron signs affecting the paraspinal musculature (e.g., torticollis from muscle weakness) may ensue, while scoliosis may develop if the muscle atrophy is severe. Unilateral epaxial cervical muscle spasms may also play a role in the scoliosis. The observation of scoliosis and cervical pain in an animal may be the first clinical sign of cervical hydrosyringomyelia. One other sign commonly seen in dogs with this lesion is persistent scratching at the neck/shoulder or flank area. Expansion of the hydrosyringomyelia centrifugally may eventually compromise the descending corticospinal/rubrospinal tracts and produce upper motor neuron signs to the pelvic limbs while extension into the dorsal columns may result in loss of proprioception.

The principal clinical signs of the cervical syndrome are listed in Table 7, and the diseases known to produce this syndrome are outlined in Table 8.

Table 7. Principal Signs of the Cervical Syndrome
<ul style="list-style-type: none"><li>• Weakness or paralysis in:<ul style="list-style-type: none"><li>- all four limbs (tetraparesis/tetraplegia) or</li><li>- limbs on the same side of the body as the lesion (hemiparesis/hemiplegia)</li></ul></li><li>• Normal or increased reflexes and muscle tone in all limbs <math>\pm</math> clasp-knife extensor rigidity in limbs on the same side as the lesion, or in all limbs</li><li>• Postural reaction deficits in limbs on the same side as the lesion or in all limbs</li><li>• Cervical muscle spasms, pain and/or rigidity (animals may resist neck flexion/extension)</li><li>• Root signature (a thoracic limb either held in partial flexion or moving in a repetitive "stamping" motion)</li><li>• Urinary incontinence</li><li>• Persistent scratching at the neck/shoulder</li><li>• <math>\pm</math> Torticollis/scoliosis</li><li>• <math>\pm</math> Respiratory difficulty</li><li>• <math>\pm</math> Horner's syndrome</li></ul>

Modified from Braund KG: An approach to diagnosing neurological disease. Waltham Focus 1999; 9:23-30 [2].

#### Notes -

a) Spinal trauma in the cervical region may be associated with cervical fractures, luxations/subluxations, or accidental penetrating injuries of the vertebral canal such as those associated with oropharyngeal stick injuries.

b) Atlantoaxial subluxation is a common cause of cervical spinal cord trauma.

c) Atlantoaxial subluxation may also occur in dogs and cats in association with occipitoatlantoaxial malformation.

d) Epidural migration of parasites, e.g., adult heartworms (*Dirofilaria immitis*) is occasionally seen in dogs producing a cervical syndrome. Spinal nematodiasis associated with *Ancylostoma caninum* may produce a similar syndrome in dogs.

e) Occipital dysplasia occurs commonly in small/medium and toy breed dogs and is usually considered to be a subclinical entity, although recent reports of hydrosyringomyelia occurring in conjunction with occipital dysplasia suggest this malformation may not be as benign as originally thought.

f) Chronic neck pain may result from oropharyngeal stick injuries and their sequelae, including cervical osteomyelitis [25].

- Spinal trauma (D + C)
- Disk disease (D)
- Cervical spondylomyelopathy (D)
- Meningitis (D)
- Atlantoaxial subluxation (D)
- Diskospondylitis (D)
- Fibrocartilaginous embolization (D)
- Hypervitaminosis A (C)



Table 8. Diseases Associated with the Cervical Syndrome	
Degenerative Disorders	Afghan Hound myelopathy; hereditary ataxia; Kooiker Dog myelopathy; Labrador Retriever axonopathy; Rottweiler leukoencephalomyelopathy
Degenerative Structural and Compressive Disorders	Calcinosis circumscripta/tumoral calcinosis; cervical spondylomyelopathy; nervous system degeneration in Ibizan Hounds; disk disease; dural ossification; Miniature Poodle demyelination; osteochondromatosis; Rottweiler leukoencephalomyelopathy; spinal synovial cysts
Developmental Disorders	Arachnoid cysts; atlantoaxial subluxation; Chiari malformations; dermoid sinus; occipital dysplasia; spina bifida; syringomyelia and hydromyelia
Endogenous Metabolic Disorders	None
Inflammatory Disorders	Abscessation; distemper; feline infectious peritonitis; granulomatous meningoencephalomyelitis; meningitis; mycotic diseases; parasitic encephalomyelitis; protothecosis; pyogranulomatous meningoencephalomyelitis; rabies; toxoplasmosis and neosporosis; leishmaniasis
Neoplasia	Spinal cord tumors
Neurotoxic Disorders	None
Neurovascular Disorders	Infarction; fibrocartilaginous embolization; hemorrhage; hemorrhagic myelomalacia
Nutritional Disorders	Hypervitaminosis A
Storage Disorders	Globoid leukodystrophy; mucopolysaccharidosis type 1
Traumatic Disorders	Spinal trauma

Modified from: Braund KG. Clinical Syndromes in Veterinary Neurology. St Louis: Mosby, 1994 [1].

### Pontomedullary Syndrome

Diseases involving the pons and medulla oblongata can produce the pontomedullary syndrome. This syndrome is characterized by the presence of multiple cranial nerve deficits in an animal showing signs of ipsilateral hemiparesis/hemiplegia or tetraparesis/tetraplegia. Ataxia may be observed in ambulatory animals. Postural reactions can be depressed in all limbs or in limbs on one side only, ipsilateral to the side of the lesion. Reflexes are intact in all limbs. Heightened muscle tone may cause limb spasticity, similar to that seen in animals with a cervical syndrome. Pontomedullary lesions involving cranial nerve nuclei and/or cranial nerves may produce a variety of clinical signs, including: jaw paralysis, masticatory muscle atrophy, decreased facial sensation, and depressed palpebral reflex (cranial nerve V; trigeminal); medial strabismus (cranial nerve V; abducent); inability to close eyelid(s), lip paralysis, ear droop, facial spasms (cranial nerve VII; facial); head tilt, rolling, nystagmus (cranial nerve VIII; vestibular); pharyngeal paralysis resulting in dysphagia and depressed gag reflex (cranial nerve IX; glossopharyngeal); laryngeal/esophageal paralysis resulting in cyanosis, dysphonia, inspiratory distress, and megaesophagus (cranial nerve X; vagus); and tongue paralysis (cranial nerve XII; hypoglossal). Mental depression may be observed as a consequence of disruption of the ascending reticular activating system (e.g., in animals with cranial trauma). In animals with severe pontomedullary lesions, several types of respiration abnormalities may be detected [7]:

- Central neurogenic hyperventilation characterized by rapid and regular respiration at a rate of about 25 per minute. This respiratory pattern is due to injury to the pons and lower midbrain, but also occurs with cerebral hypoxia/acidosis;
- Apneustic respiration, characterized by a cyclic pattern of prolonged inspiration followed by expiration and an apneic phase. This form is seen with lower brainstem (e.g., medulla oblongata) injury and carries a poor prognosis;
- Central alveolar hypoventilation characterized by shallow, slow but regular, ventilation most often seen with lesions in the medulla oblongata.

The principal clinical signs of the pontomedullary syndrome are listed in Table 9, and the diseases known to produce this syndrome are outlined in Table 10.

Table 9. Principal Signs of the Pontomedullary Syndrome	
<ul style="list-style-type: none"> <li>• Weakness or paralysis in: <ul style="list-style-type: none"> <li>- all four limbs or</li> <li>- limbs on the same side of the body as the lesion</li> </ul> </li> <li>• Normal or increased reflexes and muscle tone in all limb(s)</li> <li>• Postural reaction deficits in limbs on the same side as the lesion or in all limbs</li> <li>• Multiple cranial nerve deficits <ul style="list-style-type: none"> <li>- Jaw paralysis, decreased facial sensation (cranial nerve V)</li> <li>- Depressed palpebral reflex (cranial nerves V, VII)</li> <li>- Facial paralysis (cranial nerve VII)</li> <li>- Head tilt, falling, rolling, nystagmus (cranial nerve VIII)</li> <li>- Pharyngeal/esophageal/laryngeal paralysis (cranial nerves IX, X)</li> <li>- Tongue paralysis (cranial nerve XII)</li> </ul> </li> <li>• Irregular respiration</li> <li>• Mental depression</li> </ul>	

Modified from Braund KG: An approach to diagnosing neurological disease. Waltham Focus 1999; 9:23-30 [2].

Table 10. Diseases Associated with the Pontomedullary Syndrome	
Degenerative Disorders	Alaskan Husky encephalopathy
Degenerative Structural and Compressive Disorders	None
Developmental Disorders	Chiari malformations; intracranial intra-arachnoid cysts
Endogenous Metabolic Disorders	None
Inflammatory Disorders	Acanthamebiasis; abscessation; Aujeszky's disease; babesiosis; distemper; feline infectious peritonitis; granulomatous meningoencephalomyelitis; meningitis; mycotic diseases; parasitic encephalomyelitis; protothecosis; pyogranulomatous meningoencephalomyelitis; rabies; rickettsial meningoencephalitis; toxoplasmosis and neosporosis
Neoplasia	Brain tumors
Neurotoxic Disorders	Tetanus
Neurovascular Disorders	Infarction; hemorrhage
Nutritional Disorders	None
Storage Disorders	Fucosidosis; globoid leukodystrophy
Traumatic Disorders	Cranial trauma

Modified from: Braund KG. Clinical Syndromes in Veterinary Neurology. St Louis: Mosby, 1994 [1].

#### Notes -

- Certain primary tumors, such as medulloblastomas, choroid plexus papillomas and certain cysts (epidermoid and dermoid cysts) (See neoplasia), as well as some inflammatory diseases, including canine distemper, rabies, and the disseminated form of granulomatous meningoencephalomyelitis, have a predilection for this area of the brainstem.
- Extension of hydrosyringomyelia into the brainstem (known as syringobulbia) may produce asymmetrical cranial nerve involvement.
- Hemorrhage and edema from severe trauma to the upper cervical cord (e.g., from atlantoaxial subluxation) may extend to

the caudal brainstem resulting in multiple cranial nerve deficits

d) In animals with Chiari malformations, a small caudal fossa and cerebellar herniations into the foramen magnum would also suggest appearance of cerebellar signs (e.g., ataxia, dysmetria, absent menace response, and intention tremors); however, to date, this has not been the case, although some animals have shown ataxia and hypermetria, signs that may be related to the underlying pathology in the cervical spinal cord.

e) Multiple cranial nerves (including trigeminal, hypoglossal, glossopharyngeal) are thickened in animals with fucosidosis.

f) Multiple cranial nerve deficits may occur in Alaskan Husky encephalopathy and in animals with intracranial intra-arachnoid cysts.

g) Multiple cranial nerve stimulation may be seen in animals with tetanus.

h) Common causes of the pontomedullary syndrome seen in practice

- Cranial trauma (D + C)
- Distemper (D)
- Granulomatous meningoencephalomyelitis (reticulosis) (D)
- Rabies (D)
- Feline infectious peritonitis (C)
- Neoplasia e.g. choroid plexus papilloma (D)

### Cerebellar Syndrome

This is one of the most readily recognizable syndromes in veterinary practice. The cerebellum is a reinforcing and coordinating organ that plays an important role in harmonizing muscle contraction. Cerebellar disease results in an inability to regulate the rate, range, and force of a movement (i.e., dysmetria). Clinical signs include an exaggerated limb response when a movement is initiated, such as "goose-stepping" (hypermetria) when walking, a delayed and then exaggerated response during postural reaction testing, such as hopping and placing, or overshooting a food bowl when attempting to eat. Limb movements are typically spastic, clumsy, faltering, and jerky. The animal assumes a broad-based stance at rest, and swaying of the trunk (i.e., truncal ataxia) may be observed when the animal is walking. Initiation of movement is delayed and often accompanied by tremors (i.e., intention tremors). Tremors are especially noticeable involving the head. Intention tremors disappear at rest. Fine, pendular, or oscillatory eye movements also may be present. A bilateral menace deficit may be noted, although vision is not affected. If the lesion involves only one side of the cerebellum, the menace deficit will be ipsilateral. Anisocoria is sometimes detected in animals with cerebellar lesions. Usually the pupil contralateral to the side of the lesion will be slightly dilated. Both pupils respond normally to light directed into either eye.

Infrequently observed signs associated with specific areas of the cerebellum include opisthotonus (e.g., when a lesion involves the rostral lobe of the cerebellum), and vestibular signs (e.g., when a lesion occurs in the flocculonodular lobe or fastigial nuclear area of the cerebellum) [8].

The principal clinical signs of the cerebellar syndrome are listed in Table 11, and the diseases known to produce this syndrome are outlined in Table 12.

Table 11. Principal Signs of the Cerebellar Syndrome
<ul style="list-style-type: none"><li>• Spastic, goose-stepping gait in all limbs, especially thoracic, with preservation of strength</li><li>• Truncal ataxia</li><li>• Intention tremors of head, eyes</li><li>• Broad-based stance</li><li>• Postural reactions delayed with exaggerated responses</li><li>• Menace deficit (ipsilateral), with normal vision</li><li>• ± Anisocoria (pupil dilated contralateral to side of lesion)</li><li>• ± Opisthotonus (rare)</li><li>• ± Vestibular signs (rare)</li></ul>

Modified from Braund KG: An approach to diagnosing neurological disease. Waltham Focus 1999; 9:23-30 [2].

### Notes -

a) Congenital cerebellar disorders are either primary developmental defects/malformations or hypoplasia and atrophy secondary to an in utero or perinatal viral infection such as feline panleukopenia virus and feline parvovirus (See hydranencephaly).

b) Clinical signs in animals with spongy degeneration of the CNS (involving white or gray matter) suggest cerebellar

syndrome but other white matter and/or gray matter areas of the brain may also be affected. In Rottweilers with spongy degeneration in gray matter, signs of laryngeal paralysis may be present.

c) Clinical signs in animals with hypomyelination suggest cerebellar syndrome but white matter in other areas of the brain and/or spinal cord is also affected. Similarly with hereditary ataxia, although with this condition the signs appear to result from lesions in the spinocerebellar pathways in the spinal cord rather than in the cerebellum itself.

d) Clinical signs of Shaker dog disease suggest cerebellar syndrome but mild inflammatory lesions may also be seen in other areas of the brain.

e) Cerebellar signs are seen in some forms of multisystem neuronal abiotrophies (e.g., Cocker Spaniels, Cairn Terriers, Miniature Poodles).

f) I have listed intracranial intra-arachnoid cysts under Developmental disorders, although they also appear in the Neoplasia chapter under malformation tumors. Cerebellar signs may be seen when these cysts or other malformation tumors (such as epidermoid and dermoid cysts, teratomas, and teratoids) involve the cerebellopontine angle.

g) Cerebellar signs are not usually a clinical feature of feline ischemic encephalopathy, although cerebellar lesions may be found.

h) Puppies surviving the acute disease of canine herpesvirus encephalitis (usually resulting in sudden death) may develop cerebellar dysplasia.

i) Cerebellar signs may be seen in dogs and cats with mercury poisoning, although myriad signs of a multifocal syndrome may be present.

j) Common causes of the cerebellar syndrome seen in practice

- Congenital cerebellar disorders (C)
- Distemper (D)
- Feline infectious peritonitis (C)
- Cerebellar cortical abiotrophies (D)
- Neoplasia e.g. choroid plexus papilloma, medulloblastoma (D)

Table 12. Diseases Associated with the Cerebellar Syndrome	
Degenerative Disorders	Central axonopathy in Scottish Terriers; cerebellar cortical abiotrophies; hereditary ataxia; hypomyelination; Labrador Retriever axonopathy; mitochondrial encephalomyelopathy; multisystem neuronal abiotrophy (Cairn Terriers, Miniature Poodles); nervous system degeneration in Ibizan hounds; neuroaxonal dystrophy; spongy degeneration of the CNS
Degenerative Structural and Compressive Disorders	None
Developmental Disorders	Chiari malformations; congenital cerebellar disorders; Dandy-Walker syndrome; intracranial intra-arachnoid cysts
Endogenous Metabolic Disorders	None
Inflammatory Disorders	Abscessation; distemper; feline infectious peritonitis; granulomatous meningoencephalomyelitis; mycotic diseases; parasitic encephalomyelitis; Shaker dog disease; toxoplasmosis and neosporosis
Neoplasia	Brain tumors (e.g., malformation tumors, medulloblastomas)
Neurotoxic Disorders	Hexachlorophene; metronidazole
Neurovascular Disorders	Infarction; hemorrhage
Nutritional Disorders	Thiamine deficiency
Storage Disorders	Gangliosidosis; galactosialidosis; Gaucher's disease; globoid leukodystrophy; mannosidosis; mucopolysaccharidosis type IIIB; sphingomyelinosis
Traumatic Disorders	Cranial trauma

Modified from: Braund KG. Clinical Syndromes in Veterinary Neurology. St Louis: Mosby, 1994 [1].

### Vestibular Syndrome

The vestibular syndrome is another commonly recognized syndrome in clinical practice. Clinical signs may be caused by (a) central lesions involving the vestibular nuclei located on either side of the medulla oblongata beneath the floor of the fourth ventricle, the brainstem, or the cerebellum (central vestibular dysfunction) [9], or (b) peripheral lesions involving the vestibular portion of the eighth cranial nerve or, more commonly, the vestibular receptors in the membranous labyrinth

located within the petrous portion of the temporal bone. Vestibular disease results in loss of equilibrium. Peripheral vestibular dysfunction (PVD) is more common than central vestibular disease. Common causes of PVD in dogs and cats are congenital and idiopathic vestibular disease and otitis media-interna. Clinical signs of PVD include ipsilateral head tilt, falling, rolling, nystagmus, or walking in tight circles. There may be exaggerated extensor tone of the contralateral limbs, accompanied by decreased tone in ipsilateral limbs [10]. Strength is preserved in PVD. Nystagmus is present in the acute stages of most PVD and is usually jerking in nature with fast and slow components. The quick phase of horizontal nystagmus is in a direction away from the side of the lesion and it is the compensatory phase of the eye movement. Sometimes in animals with vestibular disease, nystagmus can be initiated by moving and holding the head in a different position (i.e., positional nystagmus). Normal, physiological nystagmus can be induced by rapid head movements in vertical or horizontal planes. The fast phase of the nystagmus is in the direction of the head movement. This response may be depressed or absent in animals with vestibular disease when the head is moved towards the side of the lesion. A ventrolateral strabismus (abnormal position of the eyeball) may be elicited in affected animals by extending the head. The strabismus is ipsilateral. Horner's syndrome and facial paralysis are frequently observed with PVD that is associated with otitis media-interna, since both facial and sympathetic nerves pass through the middle ear. Righting reactions are diminished or absent in affected animals. Presence of abnormal resting nystagmus is reportedly more commonly observed in dogs with PVD [23].

Signs of CVD in animals are similar to those seen with PVD. However, in central disease, there may be evidence of other cranial nerve dysfunction due to involvement of various brainstem nuclei (e.g., trigeminal or abducent disorders), altered mental status, vertical or positional nystagmus, cerebellar signs, and evidence of paresis and/or proprioceptive deficits resulting from brainstem involvement of descending and ascending long tracts. Note that lesions of the thalamus and/or extrapyramidal basal nuclei may also cause abnormal head posture and signs of CVD (see Diencephalic syndrome). Also, animals with CVD have a tendency to roll in one direction. Central signs do not include Horner's syndrome, although facial paresis/paralysis secondary to involvement of the facial nucleus or fibers within the facial tract may be observed. Unilateral lesions in the brainstem usually produce an ipsilateral hemiparesis and postural reaction deficiencies (associated with lesions in the general proprioceptive and/or upper motor neuron systems). However, central lesions occasionally result in a "paradoxical" vestibular syndrome in dogs in which the lesion is located on the opposite side to that expected from certain clinical signs, including head tilt, strabismus, and body tilt [11-13]. The lesion, typically a space-occupying one in the area of the cerebellopontine angle (such as tumor or granulomatous mass) is considered to be located on the same side of the body in which deficits in proprioception/postural reactions are detected. Presumably, presence of unilateral deficits of other cranial nerves would be another indicator of the side on which a lesion is located. This syndrome may occur with involvement of vestibular pathways in either the caudal cerebellar peduncle (particularly the supramedullary juxtarestiform body) or the flocculonodular lobe of the cerebellum. The paradoxical vestibular syndrome occurs less frequently in cats.

The principal clinical signs of the vestibular syndrome are listed in Table 13, and the diseases known to produce this syndrome are outlined in Table 14.

#### Notes -

- a) Brain tumors causing central vestibular disease may be surface tumors (include meningioma, choroid plexus papilloma, medulloblastoma, neurofibroma, and lymphosarcoma) or parenchymal tumors (e.g., granulomatous meningoencephalomyelitis and metastatic tumors) (also, see central vestibular disease). Forebrain tumors also may result in central vestibular disease secondary to caudal transtentorial herniation.
- b) Neoplasia is an infrequent cause of peripheral vestibular disease (see miscellaneous causes of peripheral vestibular disease).
- c) Cranial trauma may produce central vestibular disease as well as peripheral vestibular disease, e.g., secondary to fractures in the petrous temporal bone or tympanic bulla.
- d) Achiastic Black Belgian Sheep dogs have a congenital rapid pendular nystagmus with unimpaired vision (see optic nerve hypoplasia).
- e) Common causes of the vestibular syndrome seen in practice
  - Peripheral vestibular disease
    - otitis media-interna (D + C)
    - idiopathic vestibular disease (D + C)
    - drug ototoxicity (D + C)
    - congenital vestibular disease (D + C)
    - inflammatory polyps (C)
  - Central vestibular disease
    - Distemper (D)
    - granulomatous meningoencephalitis (D)
    - choroid plexus papilloma of the 4th ventricle (D)
    - toxoplasmosis (D + C)
    - mycotic diseases (e.g., cryptococcosis) (D + C)

<b>Table 13. Principal Signs of the Vestibular Syndrome</b>		
	Central Vestibular Disease	Peripheral Vestibular Disease
Loss of Balance	Yes	Yes
Head Tilt	Yes	Yes
Falling/rolling	Yes (greater tendency to roll)	Yes
Nystagmus	Yes	Yes
- Horizontal	Yes	Yes
- Rotatory	Yes	Yes
- Vertical	Yes	No
- Positional	Yes	No
Strabismus (ventrolateral)	Yes	Yes
Cranial Nerve Deficits	Possible V, VI, VII	Possible VII
Horner's Syndrome	No	Possible
Cerebellar Signs	Possible	No
Mental Depression	Possible	No
Hemiparesis with Ipsilateral Postural Reaction Deficits	Possible	No

Modified from Braund KG: An approach to diagnosing neurological disease. Waltham Focus 1999; 9:23-30 [2].

<b>Table 14. Diseases Associated with the Vestibular Syndrome</b>	
Degenerative Disorders	(Idiopathic vestibular disease); multisystem neuronal abiotrophy (Miniature Poodles)
Degenerative Structural and Compressive Disorders	None
Developmental Disorders	(Congenital vestibular disease); Dandy-Walker syndrome; intracranial intra-arachnoid cysts;
Endogenous Metabolic Disorders	Hypothyroidism;
Inflammatory Disorders	Abscessation; distemper; feline infectious peritonitis; granulomatous meningoencephalomyelitis; (inflammatory polyps); mycotic diseases; (otitis media-interna); parasitic encephalomyelitis; protothecosis; pyogranulomatous meningoencephalomyelitis; rickettsial disorders; toxoplasmosis and neosporosis
Neoplasia	Brain tumors (see notes, below)
Neurotoxic Disorders	(Aminoglycosides); metronidazole
Neurovascular Disorders	Infarction; hemorrhage; feline ischemic encephalopathy
Nutritional Disorders	Thiamine deficiency
Storage Disorders	Galactosialidosis
Traumatic Disorders	Cranial trauma

Modified from: Braund KG. Clinical Syndromes in Veterinary Neurology. St Louis: Mosby, 1994 [1]. Disorders in parentheses refer to peripheral vestibular conditions.

## Midbrain Syndrome

This is a relatively uncommon syndrome. Animals may be depressed or comatose, and there may be rigid extension of all limbs (opisthotonus). If the lesion is located on one side of the midbrain, limbs on the contralateral side will show signs of hemiparesis or hemiplegia. Ataxia may be observed in ambulatory animals. If the oculomotor nucleus and/or nerve are involved, animals will have a ventrolateral strabismus, a widely dilated pupil that is unresponsive to light stimulation in either eye, and ptosis (drooping) of the upper eyelid. These signs may be ipsilateral or bilateral, depending on the location and extent of the lesion. Vision is usually normal. Rarely, visual impairment and menace deficit contralateral to the side of the lesion may be noted in animals with lesions involving the lateral geniculate body. Central neurogenic hyperventilation characterized by rapid and regular respiration at a rate of about 25 per minute is seen in some animals associated with injury to the pons and lower midbrain. In animals with severe cranial trauma that diffusely involves the midbrain, bilateral pupillary miosis may be seen initially, with a gradual change to fixed, dilated pupils. Lesions located in the ventral midline (i.e., interpeduncular area) in cats can produce signs of obstinate progression in which cats propel themselves forward until meeting an obstacle and continue to push against it (head pressing) [14]. The principal clinical signs of the midbrain syndrome are listed in Table 15, and the diseases known to produce this syndrome are outlined in Table 16.

**Table 15. Principal Signs of the Midbrain Syndrome**

- Spastic weakness/paralysis in:
  - all four limbs or
  - limbs on the contralateral side of the body
- Increased reflexes and muscle tone in limbs on the contralateral side or in all limbs (all limbs may be held in rigid extension, i.e., opisthotonus)
- Postural reaction deficits in limbs on the contralateral side or in all limbs
- Mental depression or coma
- Ipsilateral deficits of cranial nerve III (oculomotor):
  - ventrolateral strabismus
  - dilated pupil unresponsive to light, with normal vision
  - drooping of upper eyelid (ptosis)
- Hyperventilation
- $\pm$  Bilateral miosis
- $\pm$  Obstinate progression/head pressing (cats)

Modified from Braund KG. An Approach to Diagnosing Neurological Disease. Waltham Focus 1999; 9:23-30 [2].

**Table 16. Diseases Associated with the Midbrain Syndrome**

Degenerative Disorders	Fibrinoid leukodystrophy
Degenerative Structural and Compressive Disorders	None
Developmental Disorders	Hydrocephalus
Endogenous Metabolic Disorders	None
Inflammatory Disorders	Abscessation; distemper; feline infectious peritonitis; granulomatous meningoencephalomyelitis; mycotic diseases; parasitic encephalomyelitis; protothecosis; toxoplasmosis and neosporosis
Neoplasia	Brain tumors
Neurotoxic Disorders	None
Neurovascular Disorders	Cardiac arrest; infarction; hemorrhage
Nutritional Disorders	Thiamine deficiency
Storage Disorders	None
Traumatic Disorders	Cranial trauma

Modified from: Braund KG. Clinical Syndromes in Veterinary Neurology. St Louis: Mosby, 1994 [1].

#### Notes -

a) Although intracranial intra-arachnoid cysts appear to have a predilection for the quadrigeminal cistern (typically situated above the midbrain and lying between the rostral and caudal colliculi), clinical signs of a midbrain syndrome are not seen; instead, a mass effect and cerebrocortical compression may occur leading to a cerebral syndrome).

b) Common causes of the midbrain syndrome seen in practice

Cranial trauma with midbrain compression and/or hemorrhage (D + C)

Thiamine deficiency (D + C)

Granulomatous meningoencephalomyelitis (D)

### **Diencephalic Syndrome**

The diencephalon is the caudal part of the prosencephalon (forebrain) composed of the epithalamus (habenula, pineal body), thalamus, hypothalamus, and a subthalamus (subthalamic nuclei, endopeduncular nucleus, and zona incerta) [15]. The hypothalamus is the ventral and medial region of the diencephalon forming the walls of the ventral half of the 3rd ventricle. It extends from the optic chiasm to the mamillary bodies. The hypothalamus extends ventrally as the infundibulum (pituitary stalk), a distal expansion of which is the pituitary gland. The pituitary gland (hypophysis) consists of the adenohypophysis (pars distalis, intermedia, and tuberalis) and the neurohypophysis (pars nervosa). The neurohypophysis (posterior lobe) is associated with storage and release of oxytocin and antidiuretic hormone. The adenohypophysis is concerned with secretion of somatotropins, prolactin, thyroid-stimulating hormone, gonadotropins, adrenal corticotropin, and other related peptides. Clinical signs associated with lesions of the diencephalon are uncommon, but when they occur, are most often the result of hypothalamic lesions, and usually associated with pituitary tumors. The hypothalamus is intimately involved in autonomic visceral body functions, including appetite, sexual activity, sleep-wake cycle, body temperature, blood pressure regulation, heart rate, and emotions [16]. It also regulates much of the body's endocrine activity. Animals with the hypothalamic syndrome may show signs of altered mental status (e.g., disorientation, lethargy, or coma); and/or behavior changes (e.g., aggression, hyperexcitability, pacing, wandering, hiding, tight circling, head pressing, and trembling). Gait is usually normal. Abnormal temperature regulation may be manifested as hyperthermia, hypothermia, or poikilothermia. Abnormalities in appetite are seen as hyperphagia and obesity, or anorexia and cachexia. Vision is frequently impaired if the lesion extends to involve the optic chiasm, in which case pupils may be dilated and weakly or non-responsive to light stimulation. Endocrine disturbances most often include diabetes insipidus or hyperadrenocorticism (clinical signs include polydipsia, polyuria, alopecia, pendulous abdomen, and muscular weakness). Eighty per cent or more of cases of pituitary-dependent hyperadrenocorticism in dogs are reportedly associated with a pituitary tumor (usually chromophobe adenomas). Abnormalities in carbohydrate metabolism (e.g., hyperglycemia) may also be detected in dogs and cats. In cats, pituitary acidophil adenomas have been associated with acromegaly and nervous system signs (circling and seizures), accompanied by insulin-resistant diabetes mellitus and high serum growth hormone concentrations. More than 75% of cats with Cushing's syndrome have diabetes mellitus [17]. Hemorrhages within a pituitary adenoma with secondary compression of the hypothalamus leading to "pituitary apoplexy" have been observed in a 7 year old female German Shepherd with central diabetes insipidus and hypernatremia, hyperthermia, and visual impairment [18]. Pure thalamic lesions are infrequently reported in dogs and cats, however, signs might include postural reaction deficits (contralateral), mild ataxia, visual deficits (contralateral), hypalgesia (contralateral and especially involving the head), an "adversive" syndrome (propulsive circling and head/eye deviation toward the side of the lesion) with rostral thalamic lesions, and possible disturbances in consciousness (depression, semicoma) or seizures [15]. Abnormal head/neck postures, termed "cervical dystonia" [24] have been described in dogs associated with infarction of the thalamus/subthalamus or closely related extrapyramidal basal nuclei (including caudate nucleus, pallidum and putamen). The signs ranged from head tilt (laterocollis), torticollis, retrocollis, sometimes in conjunction with nystagmus, circling and postural deficits/forelimb hypermetria. The abnormal head/neck posture may be permanent, transient or episodic. In humans, a "diencephalic syndrome" is characterized by emaciation, despite a normal or slightly diminished caloric intake, endocrine abnormalities, and a mentally alert appearance [19]. This syndrome usually occurs in infants and children and is typically associated with space-occupying lesions of the hypothalamic-optic chiasm region (especially astrocytomas). A similar condition, has been reported in a 3 year old female Doberman Pinscher associated with an astrocytoma in the rostral hypothalamus with signs of chronic weight loss with adequate caloric intake, alert mental status, bradycardia, hypothermia and lack of shiver response, lack of thirst despite negative water balance, and hypothyroidism [20]. The principal clinical signs of the diencephalic syndrome are listed in Table 17 and the diseases known to produce this syndrome are outlined in Table 18.

#### Notes -

a) Brain tumors associated with the diencephalic syndrome are most commonly pituitary tumors, although occasionally suprasellar germ cell tumors and malformation tumors (including teratomas) may be implicated. Craniopharyngiomas are rare



suprasellar tumors in dogs that may cause hypophyseal-hypothalamic injury. Extension of primary nasal cavity tumors (e.g., nasal adenocarcinoma) into the cranial vault is relatively common, and these masses may involve the base of the brain and the pituitary area.

b) Hypothalamic hamartomas are rare malformation tumors that may be associated with cataplexy-like attacks (see paroxysmal disorders, narcolepsy).

c) Contralateral hypalgesia may sometimes be found associated with lesions in the thalamic relay projections to the cerebral cortex.

d) Seizures might occur from mass lesions extending into the cerebral cortex and/or the attendant increased intracranial pressure, or from perturbations in the thalamic-cerebral cortex projection fibers, e.g., generalized absence seizures in humans [21].

e) Common causes of the diencephalic syndrome seen in practice

- Neoplasia e.g. pituitary and extension tumors (D)
- Granulomatous masses, e.g., toxoplasmosis and neosporosis, granulomatous meningoencephalomyelitis, or mycotic diseases such as cryptococcosis and blastomycosis (D + C)

**Table 17. Principal Signs of the Diencephalic Syndrome**

- Gait may be normal (hypothalamic lesions) or abnormal (ataxic) with thalamic lesions
- Altered mental status
  - disorientation, lethargy, coma
- Change in behavior
  - aggression or hyperexcitability
- Abnormal movements/postures
  - trembling, pacing, wandering, hiding, tight circling, or head pressing, cervical dystonia
- Bilateral deficits of Cranial nerve II (optic) at the level of the optic chiasm
  - visual impairment
  - dilated pupils
  - depressed pupillary reflexes
- Abnormal temperature regulation
  - hyperthermia, hypothermia, or poikilothermia
- Abnormal appetite - hyperphagia/obesity, or anorexia/cachexia
- Endocrine disturbances
  - diabetes insipidus
  - diabetes mellitus
  - hyperadrenocorticism
  - acromegaly/excess growth hormone
- $\pm$  Seizures

Modified from Braund KG. An Approach to Diagnosing Neurological Disease. Waltham Focus 1999; 9:23-30 [2].

**Table 18. Diseases Associated with the Diencephalic Syndrome**

Degenerative Disorders	None
Degenerative Structural and Compressive Disorders	None
Developmental Disorders	None
Endogenous Metabolic Disorders	None
Inflammatory Disorders	Abscessation; distemper; feline infectious peritonitis; granulomatous meningoencephalomyelitis; mycotic diseases; parasitic encephalomyelitis; toxoplasmosis and neosporosis
Neoplasia	Brain tumors

Table 18. Diseases Associated with the Diencephalic Syndrome (continued)	
Neurotoxic Disorders	Ivermectin
Neurovascular Disorders	Infarction; hemorrhage
Nutritional Disorders	Thiamine deficiency
Storage Disorders	None
Traumatic Disorders	Cranial trauma

Modified from: Braund KG. Clinical Syndromes in Veterinary Neurology. St Louis: Mosby, 1994 [1].

### Cerebral Syndrome

This commonly occurring syndrome is often characterized by abnormal movements, such as circling (usually to the same side as the lesion), continual pacing, or head pressing into a wall or cage. In some animals, the head and trunk may be twisted (pleurothotonus) toward the side of the lesion. Altered behavior and mental status are frequently observed: apathy, depression, stupor, disorientation, failure to recognize the owner or environment, loss of trained habits (e.g., house training), and sometimes aggression, or hyperexcitability. While animals may have a normal gait, postural reactions such as hopping, placing, and hemiwalking are usually depressed in the contralateral limbs. In comatose animals, breathing may be characterized by waxing and waning of the depth of respiration, with regularly recurring periods of apparent apnea (i.e. Cheyne-Stokes respiration), although the periods of "apnea" actually reflect extremely low respiratory amplitudes [22]. Vision may be impaired (bumping into objects, depressed menace reflex) on the side opposite the lesion; however, pupillary light reflexes are normal. Seizures and papilledema (edema of the optic disk, often due to increased intracranial pressure) may be observed. Seizures (see epilepsy) may be (a) generalized, with loss of consciousness and uncontrolled autonomic activity (e.g., salivation, urination, defecation, pupillary dilation, and chewing movements) and abnormal motor function (e.g., muscular rigidity, followed by running and paddling movements of the limbs), or (b) partial, where there is no loss of consciousness and where signs may indicate the location of the seizure focus, e.g., motor cortex - head turning, spasms in one limb, tail chasing; visual cortex - light or fly biting; or limbic system - confusion, viciousness, screaming, attacking inanimate objects, or fear behavior. Partial seizures may spread to become generalized seizures. The principal clinical signs of the cerebral syndrome are listed in Table 19, and the diseases known to produce this syndrome are outlined in Table 20.

Table 19. Principal Signs of the Cerebral Syndrome
<ul style="list-style-type: none"> <li>• Normal gait</li> <li>• Altered mental status (apathy, depression, disorientation, lethargy, coma)</li> <li>• Change in behavior (loss of trained habits, failure to recognize owner, aggression, or hyperexcitability)</li> <li>• Abnormal movements/postures such as pacing, wandering, circling, head pressing, twisted head and trunk (pleurothotonus)</li> <li>• Postural reaction deficits in contralateral limbs</li> <li>• Visual impairment (e.g. bumping into objects, menace deficit contralateral to side of lesion) with normal pupillary light reflexes</li> <li>• Seizures</li> <li>• <math>\pm</math> Papilledema</li> </ul>

Modified from Braund KG. An Approach to Diagnosing Neurological Disease. Waltham Focus 1999; 9:23-30 [2].

### Notes -

- In Dalmatian leukodystrophy, behavioral disturbances are not a feature.
- In the cerebral syndrome, contralateral facial hypalgesia is sometimes found, presumably associated with lesions in the somatosensory cortex or the cortical projection systems from the thalamus.
- Cerebral signs of rabies are usually associated with the "furious" form and can be very similar to those seen in dogs with post-vaccinal canine distemper encephalitis.

- d) Meningoencephalocele is usually lethal at birth.
- e) Infarction in animals is rarely seen associated with atherosclerosis (arterial xanthomatosis) but when it does occur, it may be as a complication of hypothyroidism (in dogs).
- f) Myxedema coma is an extremely rare form of decompensated hypothyroidism
- g) Common causes of the cerebral syndrome seen in practice
- Cranial trauma (D + C)
  - Hydrocephalus (D)
  - Brain tumors such as meningiomas in dogs and cats, and gliomas (e.g., astrocytomas, oligodendrogliomas) in brachycephalic dogs
  - Hepatic encephalopathy (D + C)
  - Feline ischemic encephalopathy (C)

Table 20. Diseases Associated with the Cerebral Syndrome	
Degenerative Disorders	Alaskan Husky encephalopathy; Dalmatian leukodystrophy; spongy degeneration in gray matter (Salukis); encephalomyelopathy and organic acidopathies; Yorkshire Terrier encephalopathy
Degenerative Structural and Compressive Disorders	None
Developmental Disorders	Lissencephaly; hydranencephaly; meningoencephalocele; hydrocephalus
Endogenous Metabolic Disorders	Diabetes mellitus; hepatic encephalopathy; hypernatremia; hypoglycemia; hyponatremia; hypothyroidism; uremic encephalopathy; acidosis; alkalosis; hyperthyroidism; hypophosphatemia; hypercalcemia
Inflammatory Disorders	Abscessation; distemper (see notes); encephalitozoonosis (dogs); eosinophilic meningoencephalitis; feline immunodeficiency virus encephalitis; feline infectious peritonitis; feline spongiform encephalopathy; granulomatous meningoencephalomyelitis; infectious canine hepatitis; La Crosse virus encephalitis; mycotic diseases; old dog encephalitis; parasitic encephalomyelitis; parvovirus encephalitis; Pug Dog encephalitis; rabies; toxoplasmosis and neosporosis
Neoplasia	Brain tumors
Neurotoxic Disorders	Cyanogenic plants; ethylene glycol toxicity; lead poisoning; methionine; metoclopramide
Neurovascular Disorders	Cardiac arrest; infarction; hemorrhage; feline ischemic encephalopathy
Nutritional Disorders	Thiamine deficiency
Storage Disorders	Ceroid lipofuscinosis; fucosidosis; gangliosidosis; globoid leukodystrophy
Traumatic Disorders	Cranial trauma

Modified from: Braund KG. Clinical Syndromes in Veterinary Neurology. St Louis: Mosby, 1994 [1].

### Multifocal Syndrome

In all the preceding syndromes, a single lesion is presumed to account for the clinical signs. However, a situation may arise in which an animal has signs that reflect two or more different syndromes, e.g., cerebral and lumbosacral syndromes. This indicates that more than one lesion site is present and this is termed a "multifocal syndrome".

Multifocal syndromes are usually seen in animals with infectious diseases of the nervous system. Multifocal syndromes also tend to be the hallmark of the rare, degenerative storage diseases (e.g., gangliosidosis, globoid cell leukodystrophy, etc.) which, in the majority of cases, result from a genetically-determined enzyme defect with subsequent accumulation and storage of substrates within various areas of the nervous system. Another, more common example of a multifocal syndrome is progressive, diffuse hemorrhagic myelomalacia that can develop secondary to an explosive intervertebral disk extrusion. With this disorder, an initial thoracolumbar syndrome may be followed by a lumbosacral syndrome and then by a cervicothoracic syndrome, as the lesion descends and ascends the spinal cord. Multiple clinical signs may be found in animals with brain tumors as a result of secondary changes such as cerebral edema, hemorrhage, increased intracranial pressure, obstructive hydrocephalus, brain herniations, tissue necrosis, and tumor spread within the brain. In addition, multifocal syndromes may be seen with several degenerative disorders of the CNS and are commonly encountered in animals with intoxications (see Neurotoxicities), in which signs may include excitation, depression, tremors, clonic-tonic seizures, hyperactivity, ataxia, circling, salivation, hyperthermia, and coma. Tetanic spasms involving multiple areas of the nervous system are seen in

tetanus and in strychnine poisoning, and may occur in dogs with Aujeszky's disease. The presence of constant tremors in animals is also usually indicative of a diffuse disturbance of the CNS. Tremors are typically intensified by voluntary movement. Coarse tremors of the head and body may be first seen in young animals beginning to walk as a result of congenital/hereditary disorders, such as hypomyelination of the CNS, spongiform encephalopathies (see spongy degeneration of the CNS), and central axonopathy in Scottish Terriers. Similar tremors may occur suddenly in young mature dogs, often of small white breeds (see shaker dog disease). Coarse whole body tremors can also be caused by toxins such as hexachlorophene. In conjunction with other neurological signs, tremors in dogs and cats may also be seen in a variety of diseases, including Lafora's disease, cerebellar disorders, lysosomal storage diseases, metabolic diseases (see hypocalcemia, hypoglycemia, and uremic encephalopathy), and following ingestion of certain neurotoxins such as metaldehyde (snail bait), chlorinated hydrocarbons, strychnine, organophosphates/carbamates, bromethalin, caffeine, 5-fluorouracil, levamisole, pyrethrin and pyrethroid insecticides, thallium, toluene/dichlorophen, and tricyclic antidepressants. Tremors may also accompany muscle weakness associated with peripheral neuropathies or primary myopathies. The principal clinical signs of the multifocal syndrome are listed in Table 21 and the diseases known to produce this syndrome are outlined in Table 22.

#### Notes -

- a) Too rapid correction of hyponatremia will result in multifocal clinical signs.
- b) Megaesophagus and laryngeal paralysis may be seen in dogs and cats with lead poisoning.
- c) In some animals, tetanus is characterized by stiffness in one limb before gradually spreading to involve the opposite limb and eventually, the entire body.
- d) Tick paralysis frequently results in a flaccid, ascending motor paralysis in animals.
- e) A wide variation of clinical signs commensurate with a multifocal syndrome is usually anticipated in animals with cranial trauma since lesions may be dispersed at multiple levels of the brain.
- f) Multifocal signs may be seen in animals with bacterial meningitis.
- g) While the overall incidence of CNS involvement by mycotic diseases is low, *C. neoformans* may be more likely to be incriminated than the other mycotic organisms in dogs and cats.
- h) Multifocal signs of rabies are usually associated with the "dumb" form.
- i) Protozoan encephalitis-encephalomyelitis associated with the multifocal syndrome include toxoplasmosis and neosporosis, sarcocystosis, encephalitozoonosis, trypanosomiasis, acanthamebiasis, and babesiosis.
- j) A peripheral neuropathy may be seen in animals with hypoglycemia caused by an insulinoma.
- k) Signs of cerebellar and/or vestibular syndromes may occur in animals with hydrocephalus associated with Dandy-Walker syndrome.
- l) In animals with hypomyelination, CNS lesions may be diffuse, although clinical signs appear to be mainly cerebellar.
- m) In Rottweilers with spongy degeneration in gray matter, signs of laryngeal paralysis may be present.
- n) Common causes of the multifocal syndrome seen in practice
  - Cranial trauma (D + C)
  - Granulomatous meningoencephalomyelitis (D)
  - Feline infectious peritonitis (C)
  - Toxoplasmosis and neosporosis (D)
  - Feline ischemic encephalopathy (C)
  - Hemorrhagic myelomalacia (D)
  - Neurotoxins (e.g., lead poisoning, organophosphates/carbamates, strychnine, hexachlorophene) (D + C)

**Table 21. Principal Signs of the Multifocal Syndrome**

- Presence of clinical signs that reflect two or more syndromes

**Table 22. Diseases Associated with the Multifocal Syndrome**

Degenerative Disorders	Central axonopathy in Scottish Terriers; encephalomyelopathy in young cats; encephalomyelopathy and organic acidopathies; fibrinoid leukodystrophy; hereditary polioencephalomyelopathy of Australian cattle dogs; hypomyelination; idiopathic vascular calcification; Lafora's disease; multisystem neuronal abiotrophies; spongy degeneration in gray matter (Bull Mastiffs, Cocker Spaniels, Rottweilers; Birman cats)
Degenerative Structural and Compressive Disorders	None
Developmental Disorders	Hydranencephaly; hydrocephalus

Table 22. Diseases Associated with the Multifocal Syndrome (continued)	
Endogenous Metabolic Disorders	Hypocalcemia; hypoglycemia; hyponatremia (see note); uremic encephalopathy
Inflammatory Disorders	Abscessation; Aujeszky's disease; Borna disease; distemper; eosinophilic meningoencephalitis; feline infectious peritonitis; feline polioencephalomyelitis; feline spongiform encephalopathy; granulomatous meningoencephalomyelitis; meningitis; multifocal distemper encephalomyelitis in mature dogs; mycotic diseases; parasitic encephalomyelitis; parvovirus encephalitis; protothecosis; protozoan encephalitis-encephalomyelitis (see notes); Pug Dog encephalitis; rabies; Rickettsial Meningoencephalitis; Shaker dog disease
Neoplasia	Brain tumors
Neurotoxic Disorders	Lead poisoning; hexachlorophene; mercury poisoning; organophosphates/carbamates; chlorinated hydrocarbons; tetanus; strychnine; toad toxicity; tick paralysis and various therapeutic agents/drugs (see neurotoxicities);
Neurovascular Disorders	Cardiac arrest; infarction; hemorrhage; feline ischemic encephalopathy
Nutritional Disorders	Thiamine deficiency
Storage Disorders	Ceroid lipofuscinosis; fucosidosis; gangliosidosis; globoid leukodystrophy; I-cell disease; glycogenosis type IV; mannosidosis; Niemann-Pick disease type C
Traumatic Disorders	Cranial trauma

Modified from: Braund KG. Clinical Syndromes in Veterinary Neurology. St Louis: Mosby, 1994 [1].

### Paroxysmal Syndrome

Paroxysmal syndromes encompass a group of sporadically occurring disorders that often have no structural lesions within the nervous system. Each paroxysmal syndrome tends to manifest distinctive clinical signs, and the animal is typically alert and responsive (i.e., without neurological deficits) between episodes. The pathophysiology of these disorders involves (or is considered to involve) abnormal neurotransmitter function. With the exception of epilepsy, none of these conditions is commonly seen in clinical practice. For more information on these conditions, see the chapter on paroxysmal disorders.

### Myopathic Syndrome

Over the past 10 to 15 years, myopathic disorders in both dogs and cats have become better recognized in clinical practice. Many myopathies are breed-related, and some have a predilection for males, such as the X-linked dystrophinopathies. Myopathies tend to have a bilaterally symmetrical distribution. Reflexes are usually preserved (with the notable exceptions of Labrador Retriever hereditary myopathy, nemaline myopathy in cats, animals with hyperkalemic myopathy, and in advanced cases of muscular dystrophy in dogs) and sensory perception of pain is not impaired. The myopathic syndrome is characterized by generalized weakness with animals sometimes assuming a palmigrade and/or plantigrade stance (see notes), exercise intolerance, fatigue, a stiff, stilted gait, and often, ventroflexion of the head and neck, and trismus (see notes). While gait disturbance is worsened by exercise in the majority of myopathies (often with variable return of muscle strength following rest), in certain myotonic disorders, such as those reported in Chow Chows, Staffordshire Terriers, and Miniature Schnauzers with myotonia congenita, stiffness becomes less apparent with exercise. Also, in these breeds, as well as in cats with dystrophinopathic muscular dystrophy, muscle mass is increased (hypertrophy), especially in proximal limb muscles, neck muscles and tongue. Proximal limb muscles may appear enlarged and bulging in some dogs with hyperadrenocortical (Cushing's) myopathy. Focal muscle hypertrophy may be seen in semimembranosus and semitendinosus muscles of Golden Retrievers with muscular dystrophy. In some animals, muscles appear hypertrophic because of inflammation or spasms. In many other myopathies, muscle wasting (atrophy) tends to be a feature, often generalized and including muscles of mastication. Focal masticatory muscle atrophy (particularly temporal muscle atrophy) is prominent in several myopathies, including masticatory myositis, atrophic myopathy/myositis, myositis associated with leishmaniasis, dermatomyositis, and in cats with nemaline myopathy. A temporary, dimple contracture in a muscle (e.g., limb muscle or tongue) can be induced in certain myotonic myopathies, such as myotonia congenita, following a sudden tap with the hand or percussion hammer. Muscle pain, elicited by palpation, is often present in animals with myositis/polymyositis. Limited joint movement resulting from contracture is the hallmark of certain myopathies, e.g., pelvic limb hyperextension in puppies with myositis associated with toxoplasmosis and neosporosis. Skeletal deformities such as lumbar kyphosis that may develop into lordosis by 1 year of age, curvature of the costal arch, and various muscle/limb contractures may also be observed in dogs with dystrophinopathies. Muscle contractures resulting in rigidity and extension of the pelvic limbs has been observed in one cat with congenital muscular dystrophy. Tremors and muscle fasciculations are sometimes seen in animals with myopathic disease. Some

myopathies are potentially lethal, e.g., X-linked myopathy in Golden Retrievers, hypertrophic feline muscular dystrophy, some forms of mitochondrial myopathies associated with lactic acidosis, exertional myopathy, malignant hyperthermia, and megaesophagus. The principal clinical signs of the myopathic syndrome are listed in Table 23, and the diseases known to produce this syndrome are outlined in Table 24.

Table 23. Principal Signs of the Myopathic Syndrome
<ul style="list-style-type: none"> <li>• Generalized weakness</li> <li>• Exercise intolerance</li> <li>• Stiff, stilted gait</li> <li>• Body/limb tremors</li> <li>• Localized or generalized muscle atrophy</li> <li>• Localized or generalized muscle hypertrophy</li> <li>• Dimple contracture</li> <li>• Muscle pain on palpation</li> <li>• Limited joint movement (e.g., contracture)</li> <li>• Regurgitation or altered esophageal motility (megaesophagus)</li> <li>• Ventroflexion of head and neck</li> <li>• Trismus</li> </ul>

Modified from Braund KG. An Approach to Diagnosing Neurological Disease. Waltham Focus 1999; 9:23-30 [2].

#### Notes -

- Junctionopathies, such as myasthenia gravis, may mimic signs of a myopathic syndrome.
- Devon Rex cats with hereditary myopathy often assume a unique "dog-begging" position.
- In dogs and cats with gracilis and/or semitendinosus muscle involvement, the hind-limb gait is characterized by a shortened stride with a rapid, medial rotation of the paw, external rotation of the hock, and internal rotation of the stifle during the swing phase of the stride.
- Hyperesthetic animals with hepatozoon myositis may be reluctant to move and often assume a sitting posture with rigidity of the trunk and neck ("master's voice" posture)
- One potential complication of hyperadrenocorticism is thromboembolism and signs of pelvic limb weakness, pain and collapse as a result of occlusion of the distal aorta and/or the iliac arteries.
- Potential complications of hypertrophic feline muscular dystrophy are insufficient water intake, dehydration, hyperosmolar syndrome, acute renal failure, and rhabdomyolysis.
- A plantigrade and/or palmigrade stance is also seen in Golden Retrievers with muscular dystrophy, in Rottweilers with distal myopathy, and in some dogs with nemaline myopathy. Cats with ischemic neuromyopathy often have the affected hindlimb rigidly extended early in the disease and may develop a residual plantigrade stance.
- Carpal knuckling can be a distinctive clinical feature in Burmese kittens with hypokalemic myopathy and some cats sink on their hocks.
- Joint posture is often abnormal in Labrador Retrievers with hereditary myopathy, with affected dogs having carpal overextension, carpal valgus, splaying of the digits, and a "cow-hocked" stance.
- In dogs and cats with myotonia congenita, signs are worse in cold weather and improve with exercise, while laryngeal paralysis has been noted in affected Miniature Schnauzers.
- Trismus (or lock-jaw), either partial or complete, may occur with masticatory myositis, atrophic masticatory myopathy/myositis, myotonia congenita in kittens, muscular dystrophy, myotonic myopathy, Devon Rex cat hereditary myopathy, malignant hyperthermia, myositis ossificans (localized form), and in English Springer Spaniels with dyserythropoiesis, polymyopathy, and cardiac disease.
- Tongue protrusion may be noted in feline muscular dystrophy, hyperkalemic myopathy (dogs), Cushings' disease/myotonia, and in cats with nemaline myopathy.
- I have included myasthenia gravis (MG) in the "myopathic syndrome" because of convenience; MG is a congenital or acquired disorder acting at the level of the neuromuscular junction (just as botulism and tick paralysis).
- Common causes of the myopathic syndrome seen in practice
  - Myositis associated with toxoplasmosis and neosporosis (D)
  - Masticatory myositis (D)
  - Polymyositis (D)
  - Atrophic myopathy (D)
  - Steroid/Cushing's myopathy (D)
  - Labrador Retriever hereditary myopathy (D)
  - Ischemic neuromyopathy (C)

Table 24. Diseases Associated with the Myopathic Syndrome	
Degenerative Disorders	Bouvier des Flandres myopathy; familial dysphagia; central core myopathy; Devon Rex cat hereditary myopathy; Labrador Retriever hereditary myopathy; megaesophagus; mitochondrial myopathy; muscular dystrophy; dystrophinopathies; distal myopathies; congenital muscular dystrophy; myotonic myopathy; myotonia congenita; adult-onset myotonic myopathy; secondary myotonia; nemaline myopathy; polyglucosan myopathy; congenital myasthenia gravis (see notes)
Degenerative Structural and Compressive Disorders	None
Developmental Disorders	Hypotrophic myopathy
Endogenous Metabolic Disorders	Exertional myopathy; hyperadrenocortical (Cushing's) myopathy; hyperkalemic myopathy; hypokalemic myopathy; hypothyroid myopathy; malignant hyperthermia; canine stress syndrome; secondary myotonia
Inflammatory Disorders	Hepatozoon myositis; masticatory myositis; atrophic myopathy/myositis; polymyositis; extraocular myositis; dermatomyositis; myositis ossificans (generalized); laryngeal myositis; infectious myositis; toxoplasmosis and neosporosis; drug-induced myositis; acquired myasthenia gravis (see notes)
Neoplasia	Paraneoplastic myositis; skeletal muscle tumors
Neurotoxic Disorders	Drug-induced myositis; toxic myopathy
Neurovascular Disorders	Ischemic neuromyopathy;
Nutritional Disorders	Vitamin E / selenium-responsive myopathy
Storage Disorders	Glycogenosis;
Traumatic Disorders	Fibrotic myopathy; immobilization myopathy; limber tail; myositis ossificans (localized)

Modified from: Braund KG. Clinical Syndromes in Veterinary Neurology. St Louis: Mosby, 1994 [1].

### Neuropathic Syndrome

The neuropathic syndrome is one of the more commonly observed syndromes in clinical practice, and is frequently associated with trauma of peripheral and sometimes cranial nerves (see traumatic neuropathy). The hallmarks of this syndrome are reduced or absent reflexes (hyporeflexia, areflexia), reduced or absent muscle tone (hypotonia, atonia or flaccidity), weakness (paresis), or paralysis of limb/head muscles, and after 1 to 2 weeks, neurogenic muscle atrophy. This syndrome relates to motor nerve dysfunction and as such, has been called "lower motor neuron disease" in other texts. Chronic neurogenic atrophy may result in severe fibrosis and limited joint movement from contractures (e.g., infectious polyradiculoneuritis due to toxoplasmosis or neosporosis). A variable degree of loss of sensation (hypesthesia) may be detected upon cutaneous (dermatomal) testing, since most nerves contain motor and sensory components. Tremors and muscle fasciculations (e.g., post-denervation) are sometimes seen in animals with neuropathic disease. Note that neuropathies may also be predominantly (or purely) sensory or autonomic. In animals with primary sensory neuropathies (e.g., sensory ganglioradiculitis, or breed-related sensory neuropathies in Boxers, Longhaired Dachshunds, English Pointers), the syndrome may include loss of pain sensation (anesthesia) and/or proprioception, abnormal sensitivity about the face or trunk (paresthesia), self-mutilation (perhaps as a result of paresthesia), and hyporeflexia/areflexia without muscle atrophy. While signs of autonomic nerve dysfunction, e.g., anisocoria, decreased tear secretion, bradycardia, etc., (see notes, below) are infrequently observed in animals with polyneuropathies, they are the dominant feature in dogs and cats with dysautonomia.

Traumatic peripheral neuropathies commonly involve a single nerve (i.e., mononeuropathy), such as common peroneal, radial, or facial nerves. Polyneuropathies involve several nerves, are usually bilaterally symmetrical, and are best exemplified by polyradiculoneuritis (e.g., Coonhound paralysis), in which the nerve changes show a preferential proximal distribution early in the course of the disease. Other less common degenerative polyneuropathies may also have a proximal distribution, e.g., hereditary spinal muscular atrophy in Brittany Spaniels (note that disorders of the parent cell bodies located in the spinal cord and/or brainstem are discussed under motor neuron diseases). Conversely, a distal distribution of nerve changes may be seen in several distal axonopathies ("dying-back" disorders) including several toxic neuropathies, giant axonal neuropathy in German Shepherds, and distal polyneuropathy in adult Rottweilers (see Rottweiler distal sensorimotor polyneuropathy). Pelvic limbs are usually first affected in generalized polyneuropathies. Whereas some neuropathies may have an acute (e.g., traumatic neuropathy or ischemic neuromyopathy) or subacute onset (e.g., polyradiculoneuritis), the majority of neuropathies

often are insidious in onset and have a chronic course. Chronic, relapsing polyneuropathies are becoming more commonly observed in dogs and cats. Some of these conditions are self-limiting and/or steroid-responsive. While most neuropathies involve spinal nerves, cranial nerve dysfunction may also be present in animals with polyneuropathies, e.g., facial nerve paresis/paralysis in Coonhound paralysis/idiopathic polyradiculoneuritis and hypothyroid neuropathy, and involvement of the vagus nerves (or their branches, e.g., recurrent laryngeal nerves) resulting in dysphagia/megaesophagus in German Shepherds with giant axonal neuropathy, and laryngeal paralysis/megaesophagus in young dogs with laryngeal paralysis polyneuropathy complex. Certain disorders of the neuromuscular junction, namely botulism and tick paralysis, produce signs that mimic those observed in a diffuse polyneuropathy. Metabolic neuropathies, such as diabetic neuropathy (dogs and cats) and hypothyroid neuropathy (dogs), are now well recognized, while hypoglycemic neuropathy is seen sporadically in dogs with insulinomas. Ill-defined peripheral nerve dysfunction in older dogs may be an immunological manifestation of various systemic malignant tumors (see paraneoplastic neuropathy). Nerve sheath tumors (see peripheral nerve tumors) are a relatively common cause of brachial plexus neuropathy.

The principal clinical signs of the neuropathic syndrome are listed in Table 25, and the diseases known to produce this syndrome are outlined in Table 26.

Table 25. Principal Signs of the Neuropathic Syndrome
<p><i>Motor Neuropathy</i></p> <ul style="list-style-type: none"> <li>• Flaccid paresis/paralysis of structures innervated (e.g., limb/facial muscles, esophagus, larynx, anal sphincter)</li> <li>• Neurogenic muscle atrophy</li> <li>• Reduced/absent reflexes and muscle tone</li> <li>• Muscle fasciculations</li> </ul> <p><i>Sensory Neuropathy</i></p> <ul style="list-style-type: none"> <li>• Decreased pain response (hypalgesia) or sensation (hypesthesia)</li> <li>• Proprioceptive deficits</li> <li>• Abnormal sensation/sensitivity (paresthesia) of face, trunk, or limbs</li> <li>• Self-mutilation</li> <li>• Reduced/absent reflexes <b>without</b> muscle atrophy</li> </ul> <p><i>Autonomic Neuropathy</i> (may be seen alone or in combination with sensorimotor neuropathies)</p> <ul style="list-style-type: none"> <li>• Anisocoria or dilated pupils</li> <li>• Decreased tear secretion</li> <li>• Decreased salivation</li> <li>• Bradycardia</li> </ul>

Modified from Braund KG. An approach to diagnosing neurological disease. Waltham Focus 1999; 9:23-30 [2].

#### Notes -

- Neuropathies under the "Degenerative disorders" category are hereditary or considered to be so.
- Optic neuritis is included as a "neuropathy" although the optic nerve (Cranial nerve II) is not a true peripheral nerve developmentally, structurally or in its pathological manifestations, but rather it is a tract of the CNS.
- While nutritional disorders per se have not been directly implicated in peripheral neuropathies in dogs or cats, nerve roots are often damaged secondary to exostoses encroaching on intervertebral foramina in cats with Hypervitaminosis A.
- Some forms of megaesophagus are considered to be neurogenic (e.g., in young dogs with laryngeal paralysis polyneuropathy complex).
- Neck trauma in cats may lead to Horner's syndrome and subclinical ipsilateral laryngeal hemiplegia.
- Dysphonia/laryngeal paralysis may also be observed in animals with coonhound paralysis/idiopathic polyradiculoneuritis, chronic inflammatory demyelinating polyneuropathy, in German Shepherd dogs with giant axonal neuropathy, and in dogs with sensory ganglioradiculitis and hypothyroid neuropathy.
- While many of the clinical signs of dysautonomia (e.g., dry mucous membranes, decreased tear production, mydriasis, regurgitation/constipation) suggest involvement of the parasympathetic nervous system, sympathetic nervous system dysfunction is suggested by bradycardia, hypotension, signs of Horner's syndrome (prolapsed third eyelid ptosis, enophthalmos), and distended easily expressible bladder. Note that some signs, such as proprioceptive deficits and anal



sphincter dysfunction, are non-autonomic.

h) Clinical signs of brachial plexus avulsion are predominantly those of radial nerve paralysis at the level of the shoulder.

i) Multiple cranial nerve dysfunction may be seen in dogs with fucosidosis, in cats with hyperlipidemia, and in animals with disseminated neoplasia (lymphosarcoma, leukemia).

j) Common causes of the neuropathic syndrome seen in practice

Hypothyroid neuropathy (D)

Idiopathic polyradiculoneuritis (D)

Traumatic neuropathies (e.g., brachial plexus avulsion) (D + C)

Ischemic neuromyopathy (C + D)

Toxoplasma/neospora polyradiculoneuritis (D)

Chronic relapsing inflammatory demyelinating polyneuropathy (D + C)

Idiopathic facial paralysis (D)

Table 26. Diseases Associated with the Neuropathic Syndrome	
Degenerative Disorders	Alaskan Malamute polyneuropathy; Birman cat distal polyneuropathy; congenital hypomyelination neuropathy; Dancing Doberman disease; deafness (congenital sensorineural deafness); familial German Shepherd neuropathy; giant axonal neuropathy; hyperlipidemia; hyperoxaluria; hypertrophic neuropathy; laryngeal paralysis (laryngeal paralysis polyneuropathy complex); Rottweiler distal sensorimotor polyneuropathy; progressive axonopathy in Boxers; sensory neuropathy in Longhaired Dachshunds; sensory neuropathy in English Pointers; congenital vestibular disease
Degenerative Structural and Compressive Disorders	None
Developmental Disorders	None
Endogenous Metabolic Disorders	Diabetic neuropathy; hyperadrenocortical (Cushing's) neuropathy; hypoglycemic neuropathy; hypothyroid neuropathy
Inflammatory Disorders	Brachial plexus neuropathy-neuritis; optic neuritis; polyradiculoneuritis; Coonhound paralysis; idiopathic polyradiculoneuritis; cauda equina polyradiculoneuritis; chronic inflammatory demyelinating polyneuropathy; infectious polyradiculoneuritis; trigeminal neuritis; sensory ganglioradiculitis; otitis media-interna; postvaccinal polyradiculoneuritis
Neoplasia	Paraneoplastic neuropathy; peripheral nerve tumors
Neurotoxic Disorders	Deafness (acquired sensorineural deafness); toxic neuropathies
Neurovascular Disorders	Ischemic neuromyopathy
Nutritional Disorders	None (see notes)
Storage Disorders	Gangliosidosis; fucosidosis; globoid leukodystrophy; glycogenosis type IV; mannosidosis; sphingomyelinosis (phenotypic variant of Niemann-Pick disease type A)
Traumatic Disorders	Brachial plexus avulsion; traumatic neuropathy
Unclassified neuropathies	Facial paralysis; distal denervating disease; distal symmetrical polyneuropathy; dysautonomia; idiopathic self-mutilation; idiopathic vestibular disease; sensory trigeminal neuropathy

Modified from: Braund KG. Clinical Syndromes in Veterinary Neurology. St Louis: Mosby, 1994 [1].

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## Developmental Disorders (29-Jan-2003)

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This chapter reviews the major structural malformations and developmental defects encountered in dogs and cats and their related effects on the central nervous system. Note that congenital deafness and congenital vestibular disorders are discussed with deafness and vestibular disease in the chapter on peripheral nerve disorders (See Myopathies and Neuropathies).

An outline of this chapter is as follows:

**Arachnoid Cysts**  
**Atlantoaxial Subluxation**  
**Congenital Cerebellar Disorders**  
**Chiari Malformations**  
**Dandy-Walker Syndrome**  
**Dermoid Sinus**  
**Hydranencephaly**  
**Hydrocephalus**  
**Lissencephaly**

Neuronal Heterotopia in Lagotto Romagnolos

**Meningoencephalocele**  
**Myelodysplasia**  
**Fetal Akinesia Deformation Sequence**  
**Occipital Dysplasia**  
**Optic Nerve Hypoplasia**

**Osteochondromatosis**  
**Sacrocaudal Dysgenesis**  
**Spina Bifida**  
**Syringomyelia and Hydromyelia**  
**Vertebral Anomalies**

Hemivertebra  
Block Vertebrae  
Butterfly Vertebra  
Transitional Vertebrae  
Scoliosis  
Stenosis of the Vertebral Canal  
Miscellaneous Disorders

### Arachnoid Cysts

Arachnoid cysts, also known as intra-arachnoid cysts, meningeal cysts, leptomenigeal cysts, and arachnoid diverticula, have been reported with increasing frequency over the past few years in dogs and cats [1-13]. It has been suggested that spinal arachnoid cysts in dogs most closely resemble type III spinal meningeal cysts in people [297]. As far as breed predilection is concerned, Rottweilers are often cited (in one report, 8/14 dogs were Rottweilers [297]) and the condition has been observed in related Schipperkes [7] and Shih Tzu littermates [10], suggesting an inherited etiology. The cysts are characterized as cerebrospinal fluid (CSF)-filled, dorsal midline, intradural, extramedullary cavitation lesions associated with coarse arachnoid trabeculation, that result in spinal cord compression. Occasionally, cysts located in ventral and dorsolateral locations in the cervical spinal region have been observed [14]. The cystic cavities are reportedly separated from the compressed spinal cord by an intact pia mater. In one series of affected dogs, numerous blood vessels with enlarged perivascular spaces were noted caudal to the cyst [4]. A cranial opening to the cysts, presumably continuous with the subarachnoid space and allowing flow of CSF, has been noted [7]. Usually there is no evidence of inflammation within the meninges or tissues lining the cysts, however, a mixed cellular inflammatory reaction and reactive connective tissue proliferation was reported in the cyst wall surgically removed in one case [7]. In this dog, the cyst wall was composed of pia-arachnoid meningotheial cells [7]. Many animals are less than 1 year of age, but cysts have been reported in animals up to 12 years of age. Onset of signs between 11 and 24 months was reported in one series of cases [7]. Arachnoid cysts have been observed mainly in rostral cervical and caudal thoracic/thoracolumbar sites; however, multiple cysts in the caudal cervical area of three Rottweiler dogs have been observed [14]. Cysts may also be multilobed or bilobed [297].

The pathogenesis is unknown [15] although congenital spinal dysraphism due to failure of fusion of the neural crest has been suggested [4], and indeed, in people, primary arachnoid cysts are regarded as a developmental abnormality of the arachnoid [16]. Ultrastructurally, the cyst is formed by splitting of the arachnoid membrane and the wall of the cyst is independent of the inner layer of the dura mater [16]. The wall of the cyst consists of an outer collagenous membrane and an inner layer of

cells that appear similar to normal arachnoid cells. Immunocytochemically, in people, arachnoid cysts react positively with antibody to epithelial membrane antigen, but are negative for glial fibrillary acidic protein, S-100 protein (a glial-associated protein), prealbumin, and carcinoembryonic antigen [17]. In people and in animals, arachnoid cysts reportedly may occur secondary to trauma, infection, inflammation, or subarachnoid hemorrhage [14,16]. While no evidence of trauma, other diseases, or malformations was found in Frykman's series of cases [7], disk herniation was thought to contribute to cyst formation in at least one dog in the study by Rylander's group [297].

Clinical syndromes will reflect the location of the lesion. To date, cervical syndromes and thoracolumbar syndromes have been observed. Pain is usually not a feature. Curiously, behavioral changes of depression and aggression in one Rottweiler with a C2 - C3 arachnoid cyst, disappeared following surgery, suggesting possible relief of pain [7]. Scoliosis has been reported in one dog [18]. Analysis of CSF is usually normal, although changes may include mild protein and/or mononuclear cell increase [297]. Survey radiographs tend to be non-diagnostic, although vertebral canal enlargement, possibly secondary to pressure atrophy of bone caused by the cyst [14], may be found in some cases [12]. Additionally, presence of spinal curvature, such as scoliosis, can be detected [18].

Diagnosis can be made using myelography, since the cysts usually fill with contrast agent, and there is often partial blockage to flow of the contrast medium, with associated moderate to severe (usually dorsal) spinal cord compression [19]. The cysts often appear as drop-shaped or oval contrast-filled cavities [7]. Computed tomography provides additional information on localization and lateralization of the cyst, and allows measurement of the degree of spinal cord compression [8]. Cysts may extend over several spinal cord segments. Magnetic resonance imaging may identify spinal cord parenchymal changes, such as presence of syringomyelia [8]. Sonography can be used to define the cyst wall, to characterize the internal architecture of the cyst wall, and to orientate the surgeon to the location and extent of the cyst [8]. Surgical decompression of the spinal cord appears to be the treatment of choice, using dorsal laminectomy or hemilaminectomy, in association with durotomy, drainage and/or partial excision of the cyst (surgical fenestration), and dural marsupialization often leads to permanent clinical improvement in a majority of dogs [2,4,12,13,297]; however, recurrences can occur [7,10] and neurologic deficits may persist [297]. Long-term follow-up studies (e.g., up to 4 years post-surgery) suggest that durectomy around the border of the cyst and dissecting it free from pia mater may give a more permanent recovery than durotomy and drainage [7]. Medical treatment alone, using a decreasing anti-inflammatory dosage of prednisolone, was reported to be successful in one dog [4]. Arachnoid cysts (see also intracranial intra-arachnoid cysts) have also been reported in brainstem locations, including cerebellar pontine area in a cat [20] and in the pineal region and quadreminal system of dogs [21,293].

### **Atlantoaxial Subluxation**

Atlantoaxial subluxation is instability of the atlantoaxial articulation that produces excessive flexion of the joint causing the cranial aspect of the axis to rotate dorsally into the vertebral canal with subsequent spinal cord compression often resulting in severe, acute neurological deficits. The disorder occurs most frequently in dogs and it may result from fracture, separation, absence, or malformation of the dens (odontoid process), from hypoplastic deformity of the dens along with shortening of the atlas, from fracture of the body of the axis or fracture of the atlas, from rupture or stretching of the atlantoaxial ligaments with an intact normal dens, or from absence of the transverse ligament of the atlas [22-30].

The pathogenesis of the developmental malformations remains uncertain. Anatomical studies indicate that the dens develops from 2 separate ossification centers [31]. In this report, the authors suggested that dens dysplasia was unlikely to be a result of failure of development of one of the ossification centers but that vascular-related ischemia might lead to postnatal resorption of at least the middle part of the dens and result in dens dysplasia with subsequent atlantoaxial subluxation [31]. While hereditary factors may be involved in some lines of miniature and toy breeds of dogs in which this congenital anomaly is most common (e.g., Yorkshire Terrier, Chihuahua, Pomeranian, Japanese Chin, Toy Poodle, Pekingese, etc.), fracture and insufficient ligamentous support of the dens may occur in any breed. The condition has been reported as a congenital disorder in several large breeds, including Rottweiler and Doberman Pinscher [32,33]. Congenital atlantoaxial subluxation occurs most commonly in dogs less than one year of age; however, older animals exposed to various stresses also may be affected. Atlantoaxial subluxation has been sporadically reported in cats [34-36]. Atlantoaxial subluxation may also occur in dogs and cats in association with occipitoatlantoaxial malformation (OAAM) [37-39], a congenital deformity of the upper cervical spine that is characterized by absence of occipital condyles with fusion of the atlas to the occiput and hypoplasia of the atlas, axis and dens [40]. The atlanto-occipital and atlantoaxial joints are regarded as a single complex on both anatomical and biomechanical grounds [40,41]. Fusion of the atlanto-occipital joint may exacerbate instability of the atlantoaxial joint and complicate surgical attempts to correct it [42]. Atlantoaxial subluxation associated with dorsal dens angulation [43] and abnormal occipitoatlantal articulation [44] have been seen in adult Cavalier King Charles Spaniels with Chiari malformations.

Clinical signs vary according to the degree of luxation. They may range from cervical rigidity and pain to spastic paraparesis, and sometimes tetraplegia (see cervical syndromes). The signs may develop slowly over several months or they may occur

acutely. In some instances, hemorrhage and edema from severe trauma to the upper cervical cord may extend to the caudal brainstem resulting in cranial nerve deficits [45] (see pontomedullary syndrome).

When atlantoaxial subluxation is suspected, survey radiographs should be made without anesthesia before manipulating the animal excessively. Lateral view radiographs will reveal widening of the space between the arch of the atlas and spinous process of the axis, angulation of the axis relative to the atlas, a fractured dens, or the rounded end of the axis indicating the absence of the dens. Oblique lateral or ventrodorsal views may be useful in determining the presence or absence of the dens. Open mouth frontal and flexed lateral views are not necessary in most cases and are likely to cause severe compression of the spinal cord [46]. Use of specialized neuroimaging techniques, including computed tomography (CT) and computed tomographic myelography, are also recommended [14,47].

The prognosis is guarded. In a recent study on risk factors affecting the outcome of surgery for atlantoaxial subluxation in 46 dogs, an age of onset less than 24 months, duration of clinical signs less than 10 months, and preoperative neurological status were found to be significant positive prognostic factors [48]. In an earlier surgical study involving 23 dogs with atlantoaxial subluxation, only 4 of 7 non-ambulatory dogs recovered [49]. A potential complication from myelography and/or surgical manipulation in animals with atlantoaxial subluxation is cardiopulmonary arrest [50,51]. Medical treatment involves similar protocols as outlined under acute spinal trauma. Neck and head splinting in extension for animals with mild luxations and cervical pain or minimal neurological deficits followed by cage rest for at least 6 weeks has been successful [14,45,52]. Internal stabilization of the luxation generally is regarded as the therapy of choice [53], especially in animals with moderate to severe neurological deficits or in animals treated conservatively having recurring episodes of pain. Results of several studies [49,54] suggest that vertebral stabilization using a ventral approach [55] may be safer than dorsal stabilization of the atlas and axis. The application of ventral pins and polymethylmethacrylate has been used successfully in the surgical treatment of congenital and traumatic atlantoaxial instability [56,294]. In one case report involving an 8 month old Rottweiler with hypoplasia of the dens, use of cannulated screws was considered superior to K-wires and conventional screws for arthrodesing the atlantoaxial joint [57]. Stabilization with bone plates via a ventral approach has been successful in dogs [51]. The subluxated atlantoaxial joint of a tetraplegic Yorkshire terrier was reduced and secured in position by means of a novel cross pinning technique applied via a dorsal approach [58]. Use of the nuchal ligament as a means of securing the spinous process of the axis to the dorsal arch of the atlas has also been reported to be successful in small- and large-breed dogs [59]. In dogs and cats with OAAM, a combination of substantial internal and external fixation, odontectomy, and arthrodesis of the atlantoaxial articulation is recommended [39,42]. Poor results have been reported [60] using the Kishigami atlantoaxial tension band [61].

### **Congenital Cerebellar Disorders**

Congenital cerebellar abnormalities tend to be either:

- a. Primary developmental defects or malformations or
- b. Hypoplasia and atrophy secondary to an *in utero* or perinatal viral infection [62].

As with most other congenital anomalies, malformations of the cerebellum in domestic animals usually result from unknown causes. Various forms of cerebellar agenesis (absence of the whole or parts), aplasia (faulty development with no tissue differentiation) and cerebellar hypoplasia (faulty development with some tissue differentiation), have been reported in dogs, including Beagle, Silky Terrier, Airedale Terrier, Chow Chow, Irish Setter, Boston Terrier, Bull Terrier, and Wire-Haired Fox Terrier [63-68]. The Wire-haired Fox Terriers and Irish Setter puppies also had lissencephaly [65]. An unusual, probably inherited cerebellar cortical dysplasia has been reported in St. Bernard puppies characterized by abnormal laminar cytoarchitecture of the cerebellar cortex: loss of distinction between granule cell, Purkinje cell or molecular layers along with pallor and cavitation of the subcortical white matter of cerebellum and cerebrum [306]. Cerebellar abiotrophy (see cerebellar cortical abiotrophies) is a post-natal degenerative disorder associated with an intrinsic developmental abnormality of various neurons, especially Purkinje cells, causing their premature death [62]. Affected animals are normal at birth or at the time they first begin to ambulate (around 3 to 4 weeks of age) [65]. Occasionally, a neonatal cerebellar abiotrophy is seen in which animals show cerebellar signs at birth [65,69]. The cerebellum may also be involved with heterogeneous developmental disorders seen in animals with Dandy-Walker Syndrome and Chiari malformations.

*In utero* infection with feline panleukopenia virus (parvovirus) results in destruction of actively dividing cells in the external germinal layer, which is actively proliferating at birth and for the first 2 weeks postnatally [70-73]. Postnatal infections with this virus rarely involve the central nervous system; however, since the cerebellum continues to develop postnatally, viral infection at birth might be expected to result in significant cerebellar hypoplasia [62]. Gross cerebellar lesions vary from marginal overall reduction in size to extensive loss of cerebellar tissue and associated reduction in size of the transverse fibers in the pons and the pontine nuclei [62]. Microscopically, lesions range from mild granulo-prival hypoplasia (depletion

of granule cells and heterotopia of Purkinje cells within narrowed molecular layers) to rudimentary folia without any neurons [62,70,71]. Rarely, other developmental anomalies can occur in affected kittens, such as hydrocephalus (from aqueductal stenosis) and hydranencephaly. Infrequently, perivascular necrosis and mineralization in cerebral internal capsules or periventricular tissues may be observed [62]. Cerebellar agenesis or hypoplasia in conjunction with hydrocephalus and hydranencephaly has also been reported in kittens secondary to *in utero* parvovirus infection, possibly due to vaccination that occurred late in the first, or early in the second, trimester of pregnancy [74]. To date, a comparable viral-related cerebellar disorder is less clearly defined in dogs, although microscopic lesions similar to those seen in cats following *in utero* viral infection was observed in a young adult Beagle [62,65]. Further, results of recent molecular studies suggest that cerebellar hypoplasia may be associated with *in utero* parvoviral infection in dogs [295].

The signs of cerebellar disease are generally symmetrical and include limb spasticity, dysmetria, head tremor, truncal swaying, loss of balance, and wide-based stance. Some animals have difficulty standing and are unable to take more than a few steps without falling [65]. Ataxia in Samoyeds with neonatal cerebellar abiotrophy is most severe in pelvic limbs with marked spasticity and hypermetria. Irish Setter puppies with HQA are unable to walk. Abnormal nystagmus is unusual in these conditions [65], although it was observed in Irish Setter puppies with HQA [69]. Generalized seizures were observed in one Wire-Haired Fox Terrier with cerebellar malformation and lissencephaly after reaching one year of age [65]. Signs in St. Bernard puppies included inability to stand, spontaneous searching nystagmus, ventrolateral strabismus, and occasional thoracic limb paddling movements [306].

Diagnosis of congenital cerebellar disorders usually is based on age, breed/species, history (e.g., of viral infection), histopathology, immunofluorescence, or DNA studies using polymerase chain reaction. It has recently been shown that parvoviral DNA can be amplified from archival and fresh tissues from both cats and dogs with cerebellar hypoplasia [295]. As the condition usually is non-progressive, prognosis for longevity may be favorable. There is no treatment.

### **Chiari Malformations**

Chiari malformations are complex developmental disorders involving the caudal brainstem, cerebellum and cranial cervical spinal cord. In people, Chiari malformations have been divided into two types based on severity of the hindbrain deformity [75]. In patients with Chiari I, there is elongation and caudal displacement of the cerebellar tonsils (vermis and paravermis lobes) and sometimes, part of the medulla oblongata, through the foramen magnum into the cranial cervical vertebral canal. The cord, pushed caudally by medulla and the fourth ventricle, is kinked. Hydrosyringomyelia (this term is used to denote presence of either syringomyelia or hydromyelia since it is often impossible to differentiate syringomyelia and hydromyelia using imaging techniques [76], although some authors prefer the term "syrinohydromyelia") may be associated with the Chiari I malformation and may develop secondary to overcrowding of the foramen magnum and obstruction of CSF flow, although its pathogenesis remains unclear. In Chiari II patients, there is herniation of the cerebellar vermis and sometimes, the inferior lateral cerebellar hemispheres, over the dorsal aspect of the cervical spinal cord. The fourth ventricle, pons, and medulla are also elongated and partially located in the spinal canal, usually in association with meningocele [75].

Chiari I malformations, similar to those in people, have been described in dogs [43,44,76-78]. The condition is over represented in Cavalier King Charles Spaniels (CKCS) and a familial/genetic basis is suspected, most likely of autosomal recessive inheritance [299]. It has been reported also in a Maltese Poodle [76]. The condition in CKCS appears to be associated with occipital bone hypoplasia which results in caudal fossa overcrowding, obstruction of CSF pathways and secondary hydrosyringomyelia [299]. Trauma superimposed on a pre-existing Chiari type 1 congenital abnormality may play a role in some clinical cases [44]. In published reports, the age range of affected animals extends from 6 months to 10 years. The clinical course may be acute [76] or run an extended course over several months or years [43,44,78].

Clinical signs may include cervical pain, torticollis, spinal hyperesthesia, exercise intolerance, paresis in one or both thoracic limbs or tetraparesis, ataxia/hypermetria in thoracic or in all four limbs, bunny-hopping hindlimb gait, poor hopping responses, and proprioceptive deficits. Spinal reflexes may be exaggerated. In a recent study of affected CKCS, a variety of cranial signs were also seen, including facial nerve deficits (9/22 dogs), seizures (7/22 dogs), and vestibular syndrome (7/22 dogs) [300]. Paroxysmal involuntary flank scratching, sometimes extended over several years, has been noted in CKCS, of either gender, usually between 6 months and 2 years of age [77,78,299]. There is no dermatologic cause and the scratching seems to be intensified by excitement, barking, exertion, wearing of collars, or when the shoulder, neck or ear of the "scratched" side are touched [77,78]. Affected animals often showed evidence of pain or hyperesthesia around the neck, ear or thoracic limb. This unusual scratching feature may be due to disinhibition of hindlimb reflex activity [44] or to some form of paresthesia secondary to the hydrosyringomyelia [78] (that was present in all 7 dogs of this study and all of whom manifested this peculiar scratching reaction), possibly related to interruption of the decussating spinothalamic tracts and dorsal/ventral horn damage due to a progressively expanding hydrosyringomyelia [44,78]. Interestingly, hydrosyringomyelia was lacking in one report in a CKCS, in whom the persistent flank scratching was not present [43]. Variable lower motor neuron deficits, such as muscle atrophy, weakness, and decreased spinal reflexes, have been noted in several dogs, especially affecting the thoracic limb ipsilateral to the "scratched" side [78]. Presumably, these signs of a cervicothoracic syndrome

could be explained if the hydrosyringomyelic lesions extended to low cervical and cranial thoracic cord levels. Denervation of spinal epaxial muscles may lead to muscle atrophy and scoliosis [18,79] and, when cervical muscles are involved, torticollis. Electromyographic studies may reveal evidence of denervation in paraspinal and thoracic limb muscles [78]. Analysis of CSF in animals with Chiari I malformation may be normal or show a mild, mononuclear pleocytosis. Radiographs of skull and cervical spine are usually normal, however, cervical scoliosis has been observed [78], and in another case, radiography revealed a developmental angulation of the dens with spinal cord compression and scalloping of the dorsal arch of C1 [43]. Magnetic resonance imaging (MRI) may show varying degrees of ventricular enlargement/hydrocephalus, hydrosyringomyelia of cervical spinal cord that occasionally is seen to extend all the way to the caudal lumbar spinal cord segments, and sometimes, caudal displacement of the caudal lobe of the cerebellum to the level of or through the foramen magnum [43,44,76,78,300]. In one series of cases involving the CKCS, the foramen magnum was small using MRI and the shape of the caudal fossa was abnormal due to a rostral indentation of the occipital bone, leading to overcrowding within the foramen magnum and apparent compression of the brainstem at the cervicomedullary junction [78]. Additionally, the tentorium cerebelli appeared more horizontal than normal, the caudal medulla oblongata had a kinked and elongated appearance, and the dorsoventral diameter of the craniocervical vertebral canal was small [78]. In other dogs, there may be abnormal alignment of the occipito-atlantal articulation and dorsal displacement of the caudal medulla and C1 spinal cord segment. MRI studies in CKCS have also revealed that the malformation may also be clinically silent in some dogs [300].

Treatment has been empirical with variable success. In one dog, furosemide (2 mg/kg, bid, over a 2-week period) resulted in moderate neurological improvement, reduced frequency of paroxysmal scratching episodes, and clinical stability 3 years after diagnosis [44]. In the study of 7 CKCS [78], low levels of oral prednisone (0.5 mg/kg PO every other day) and dexamethasone (0.25 to 0.5 mg, PO sid or every other day) provided an initial mild improvement in neurological signs that subsequently remained stable or slowly deteriorated. Use of neuralgesics carbamazepine and amitriptyline was unsuccessful. Carprofen (2mg/kg PO bid) had some temporary effect but was considered to be less effective than the glucocorticoids. Meloxicam (0.1 mg/kg PO sid) improved clinical signs in one dog. More recent studies of CKCS suggest that mild cases may not require treatment or may be managed using non-steroidal anti-inflammatory agents [299], while surgical management (eg, subtotal occipital craniectomy with durotomy to relieve obstruction at the level of the foramen magnum) for dogs with progressive signs. A surgical subdural shunt draining to the abdomen has also been successfully employed (Dr. G. Skerritt, personal communications, 2002). Anti-inflammatory doses of prednisolone are recommended for dogs where surgery is not possible or results in limited improvement [299].

### **Dandy-Walker Syndrome**

The eponym, Dandy-Walker syndrome, refers to complex heterogeneous developmental anomalies in people characterized by the morphological triad of aplasia or hypoplasia of the cerebellar vermis (especially the caudal portion), cyst-like dilatation of the fourth ventricle, and hydrocephalus [75]. The Dandy-Walker syndrome is believed to be a disorder of fusion of dorsal midline structures of the primitive neural tube [80]. Failure of development of the midline portion of the cerebellum forms the basis of this syndrome with subsequent enlargement of the posterior fossa, abnormally high placement of the tentorium, and elevation of the transverse sinuses. The syndrome may also be associated with syringomyelia and agenesis of the corpus callosum. A similar syndrome has been reported in several breeds of dogs including Beagle, Silky Terrier, Chow Chow, Tervuren, Boston Terrier, Briard, Labrador Retriever, Bull Terrier, Weimaraner, and Dachshund [64,81,82] and in a Domestic shorthair kitten [83]. Cases are characterized by cerebellar vermian aplasia or hypoplasia, often associated with a fluid-filled, cyst-like structure in continuity with a dilated fourth ventricle that fills the posterior fossa. A communicating hydrocephalus is frequently present. The pyramis, uvula, and nodulus cerebellar lobules were commonly involved in several reports involving dogs [64,82]. Additionally, portions of the cerebellar hemispheres and flocculus can be affected. Microscopic changes may include focal or scattered Purkinje cell chromatolysis and atrophy, indistinct deep cerebellar nuclei, scattered axonal spheroids, and reduction of granule cells in the cerebellar cortex. Retrograde transsynaptic neuronal degeneration, such as chromatolysis or vacuolation of neurons, may be noted in brainstem nuclei that project to the cerebellum, including olivary, lateral reticular, lateral cuneate and vestibular nuclei. The lateral apertures through which the fourth ventricle communicates with the subarachnoid space appear to be microscopically normal in dogs [82]. Similarly, no evidence of foramenal atresia was found in the affected kitten [83]. The wall of the posterior fossa cyst may be lined by pia-arachnoid, neuropil, and an inner layer of flattened ependymal cells [64] or by ependymal cells alone [82]. Hydromyelia is not usually a feature but has been reported in two adult dogs [76]. A comparison of pathological features seen in animals with Dandy-Walker syndrome and Chiari I malformation is shown in Table 1.

Table 1. Comparison of features of Chiari I malformation and Dandy-Walker Syndrome in dogs *.		
	Chiari I Malformation	Dandy-Walker Syndrome
Hydrocephalus	Variable	Common
Fourth Ventricle	Normal	Cystic and may descend into cervical cord
Cerebellum	Ectopic	Hypoplasia / aplasia
Cerebellar position	caudal displacement of the caudal lobe of the cerebellum to the level of or through the foramen magnum	Normal
Posterior fossa cysts	None	Present
Hydromelia	Common	Uncommon
Meningomyelocele	None	None

\*Modified from Kirberger RM et al., [76].

Clinical signs of ataxia, dysmetria, absent menace response, and intention tremors reflect a cerebellar syndrome. In addition, some animals with flocculonodular lobe lesions may show a vestibular syndrome, such as head tilt, nystagmus, ventromedial strabismus, circling, and falling. Seizures, behavioral abnormalities and visual impairment may be seen in animals with hydrocephalus [82,83]. A bunny-hopping gait was observed in one 12 week old Beagle [64]. Clinical signs tend to be non-progressive and may be seen in young animals as early as 2 weeks of age or may be delayed until 3 or 4 months of age. The condition has also been reported in adult dogs: a 4 year old Cavalier King Charles Spaniel and a 2.5 year old Maltese Poodle with signs of intermittent pain and paresis/hypermetria, respectively [76]. The 4 month old kitten was presented with acute-onset collapse and lethargy. Signs of stupor, intermittent rotatory nystagmus, partially constricted pupils, lack of menace response, but with normal pupillary light reflexes, were noted. Tactile and visual placing reactions were diminished. Late-onset aggression occurred in this kitten [83].

Analysis of cerebrospinal fluid is normal. Radiographic studies may reveal a very thin and dome-shaped calvarium with a smooth "ground glass" appearance, suggestive of hydrocephalus. Scalping of the inner table of occipital bone was observed in one dog [81]. A dilated ventricular system and cystic dilatation of the fourth ventricle can be identified using MRI [76,83] or cisternography [81]. Hydromyelia was diagnosed in two adult dogs using myelography and MRI [76].

Prognosis depends on severity of clinical signs. If the signs are mild, prognosis for longevity and quality of life may be good, especially since signs tend to be non-progressive. Ventriculoperitoneal shunting was performed in the kitten that did well for 13 weeks before its condition deteriorated [83].

### Dermoid Sinus

A dermoid sinus, also termed pilonidal sinus, pilonidal cyst or dermoid cyst, is a neural tube defect resulting from incomplete separation of skin and neural tube during embryonic development. Dermoid sinus was once considered to be unique to the Rhodesian Ridgeback breed or Ridgeback crosses [84-90], however, the condition has now been reported in several breeds of dogs [91-96] and rarely in cats [97,98]. It is believed that the sinus is hereditary in nature in Ridgebacks, probably as a simple autosomal recessive gene.

The dermoid sinus typically occurs in the dorsal midline in the cervical, cranial thoracic, and sacrococcygeal regions. One or more may occur in the same animal. The sinuses form a small external opening about 1 mm in diameter and the hair around the orifice is concentrated in a little tuft. The sinus is lined by modified skin, incorporating hair follicles and sebaceous glands, so that the lumen contains hair, exfoliated cells, and sebum. There may be histological evidence of a pyogranulomatous foreign body-type reaction to hair fragments and other debris. The sinus runs from the skin toward the supraspinous ligament to which it may or may not be attached by fibrous tissue. Occasionally, the sinus may extend through the vertebral canal to communicate with the dura mater and subarachnoid space, especially in the sacrococcygeal region, and less commonly in the thoracic and cervical regions. This seems to be the case for Rhodesian Ridgeback dogs, but may be seen in other breeds too [91]. There is the suggestion, based on limited case numbers, that dermoid sinus in non-Rhodesian Ridgeback breeds may occur more commonly in cranial thoracic (e.g., T1 - T4) [92,93,96] or mid thoracic regions (e.g., T6 -



T7) [93], and that there may be a proportionally higher prevalence for dermoid sinus-dural mater communication in these breeds [91]. The dermoid sinus occurred at T3 vertebral level in the affected cat [98]. In the cervical area, the sinus is commonly attached to the area of the spinous process of the second cervical vertebra. In one report, a C2 transosseous communication with the vertebral canal was reported in a Rhodesian Ridgeback/Dalmatian cross [87]. Some dogs with dermoid sinus have other congenital anomalies as spinal cord myelodysplasia [96] and vertebral anomalies including rachischisis, vertebral fusion, and hemivertebra [91,93].

The sinus tract is often palpable as a firm cord of tissue that continues ventrally to the level of the dorsal spinous processes of the underlying vertebrae [91]. An exudate may be seen emanating from the skin orifice. Neurological signs can occur in dogs at any age when the sinus communicates with the subarachnoid space and becomes infected, leading to meningitis, myelitis, or spinal cord compression. To the author's knowledge, only a single case of spinal cord involvement has been reported in cats (in a 16 month old Balinese cat, at the level of the third thoracic vertebra) [98]. According to the location of the sinus, and degree of involvement of the spinal cord and/or meninges, neurological signs may reflect either a cervical syndrome, cervicothoracic syndromethoracolumbar syndrome, or lumbosacral syndrome. Not every animal in which the sinus communicates with the subarachnoid space will show clinical or neurological deficits [89]. Various organisms, including *Staphylococcus intermedius*, may be cultured from the sinus. Analysis of CSF may reveal increased protein content and elevated white cell count if there is an underlying meningitis/myelitis present [91]. Radiography can be used to identify presence of any vertebral anomalies, while contrast studies such as fistulography/sinography (e.g., using a non-ionic contrast medium, such as Omnipaque) may help determine the extent of the sinus, the central region of which may be enlarged to form a cyst-like cavity. Myelography can be used to detect the presence of meningeal abnormalities and possible spinal cord compression [93,96]. The sinus and adjacent vertebrae may also be characterized using special imaging techniques, including computed tomography and ultrasonography [87,93]. In one dog, computed tomography identified schisis (cleft) of the T7 dorsal arch, displacement of the spinal cord and dural sac, and the dermoid sinus dorsal to the vertebra [93]. Surgical excision, typically in conjunction with dorsal laminectomy, is the treatment of choice, along with appropriate antibiotic therapy based on culture of the sinus and sensitivity testing. Prognosis is guarded, as recurrence of infection may occur with incomplete surgical removal [87].

Nasal dermoid sinus cysts, rare developmental defects, and characterized by intermittent discharge from a small opening in the midline on the bridge of the nose at the junction between the nasal planum and the skin, have been reported in dogs (3 of 6 dogs were Golden Retrievers). These cysts have the potential for extending into the cranial vault causing cerebral abscesses or recurrent meningitis. Complete surgical excision has a good prognosis.

### **Fetal Akinesis Deformation Sequence**

A lethal developmental disorder called fetal akinesis deformation sequence has been described in a breeding colony of dogs that is inherited as an autosomal recessive trait [301]. Fetal akinesis was demonstrated by abdominal ultrasonography of late-gestation bitches. Puppies died at birth due to respiratory failure and exhibited scoliosis and arthrogryposis. Grossly, changes included microencephaly, small cerebellum and brainstem, reduced caudal cerebral sulcation, thin spinal cord, and generalized neurogenic muscle atrophy. Neuronal degeneration and gliosis were found in spinal cord, brainstem nuclei, and cerebellum in which there was reduced foliation, marked loss of Purkinje cells in some folia, loss of cells in the external granular layer, and absence of cells in the deep cerebellar nuclei. The cerebral cortex had normal layers but with reduced cell numbers. The condition is thought to be associated with slowing or arrest of CNS development due to accelerated neuronal degeneration in mid to late gestation, with the ensuing neurogenic fetal immobility causing contracture of skeletal muscles leading to global arthrogryposis and respiratory failure at birth. The disorder is considered to resemble pontocerebellar hypoplasia type I in humans, an autosomal recessive neurodegeneration disorder associated with anterior horn cell disease and neurogenic muscle atrophy [302].

### **Hydranencephaly**

Hydranencephaly and porencephaly are rare, related malformations associated with failure of development (hypoplasia) and destruction (secondary atrophy) of primarily the neopallial part of the telencephalon (the neocortex and the ventricular zone) [62,99,100]. Dogs and cats may be affected. The pathogenesis of this anomaly is not always certain. In people, a fetal cerebrovascular accident may result in massive necrosis and resorption of tissue [99]. In animals, the most common cause is *in utero* viral infection [62,100]. While many different viruses (including Akabane, Bluetongue and Rift Valley fever) are implicated in large animals, hydranencephaly in cats has been linked with vaccine-induced intrauterine feline panleukopenia / parvovirus infections [74,101]. Porencephaly refers to the occurrence of single or multiple cystic cavities in the cerebrum, usually communicating with the lateral ventricles or subarachnoid space. According to Summers and colleagues [62], porencephaly might occur if infection occurs later in the period of fetal nervous system vulnerability or if it is less destructive. Hydranencephaly is characterized by virtual absence of the cerebral hemispheres usually with preservation of

olfactory and hippocampal components, fornix, and basal nuclei [62]. The cerebral hemispheres are replaced by cerebrospinal fluid-filled sacs lined by leptomeninges, a glial membrane, and ependymal remnants. Microphthalmia has been reported [102] and there may be loss of nerve fibers and reduced myelin staining in optic nerves. Other structures including the brainstem and cerebellum may or may not be affected. In kittens with *in utero* parvovirus infection, hydranencephaly occurred in conjunction with cerebellar agenesis and hypoplasia [74]. Involvement of structures other than the cerebral cortex may depend on the developmental stage of the nervous system at the time of fetal infection.

Clinical signs are usually seen within several weeks after birth and depend upon nervous structures involved. Animals with predominant cerebral cortex involvement may have behavioral changes, including dummy-like characteristics, indifference to their environment, and episodes of rage, are usually blind, and may be unable to suckle. Urinary and fecal incontinence may be present. In animals with cerebellar involvement ataxia, dysmetria, and difficulty standing may be noted. Other animals can appear active but have difficulty in prehending food and drinking water. Unilateral hydranencephaly has been observed in an 8-month old Miniature Poodle whose only clinical sign was a visual defect [100]. Accordingly, prognosis varies from guarded to poor. Diagnosis is suggested by clinical signs and neuroimaging techniques, such as MRI, and confirmed by histopathology, immunofluorescence, or DNA studies using polymerase chain reaction [74].

### Hydrocephalus

Hydrocephalus is one of the most common manifestations of developmental disorders in dogs and cats [103-105] and is the result of a disturbance in the normal cerebrospinal fluid (CSF) fluid dynamics [75]. It is characterized by increased CSF volume and dilatation of the cerebral ventricles. It may be congenital or acquired postnatally. It may occur passively in which the increased volume of CSF fills voids left by loss of brain parenchyma [106]. This has been called compensatory hydrocephalus or hydrocephalus ex vacuo and is often seen with congenital defects or malformations, such as hydranencephaly and cerebellar hypoplasia, and may follow severe destructive parenchymal lesions, such as cranial trauma or ischemic encephalopathy in adult cats [107]. The most common form of hydrocephalus in animals is obstructive (non-communicating) hydrocephalus [108] typically caused by obstruction to CSF flow in the intraventricular pathway, in which ventricular dilatation occurs proximal to the obstruction site, with preservation of normal ventricular size distal to the block. Obstruction may also occur at the point of CSF resorption by the arachnoid villi in the subarachnoid spaces (e.g., meningitis, malformation of arachnoid villi, or tumors compressing the venous sinuses [107]). CSF pressure tends to be increased (hypertensive) in cases of obstructive hydrocephalus [107]. While obstruction may occur anywhere along the ventricular pathway in congenital hydrocephalus, it occurs most commonly in the mesencephalic aqueduct of Sylvius. Obstructive hydrocephalus in dogs and cats may be associated with various developmental defects, e.g., myelodysplasia, Dandy-Walker syndrome, spina bifida, syringomyelia and hydromyelia, optic nerve hypoplasia, occipital dysplasia, craniofacial abnormalities in Burmese cats [109], polymicrogyria in Poodles [110], triploidy (a fatal condition characterized by the presence of three haploid sets of chromosomes, instead of two, in all cells) in a stillborn puppy [111], aphakia (absence of the lens) and multiple ocular defects in Saint Bernard puppies [112], and griseofulvin teratogenesis [113], as well as intra-uterine infectious diseases such as parvovirus [74] and panleukopenia virus [114]. Postnatal, acquired obstructive hydrocephalus, again often involving the mesencephalic aqueduct, has been associated with feline infectious peritonitis [115-117], parainfluenza virus [118,119], necrotizing periventricular encephalitis [120-122], cryptococcal granulomatous ependymitis [123], methylmercury poisoning [124], parasitic migration [125,126] and occasionally it may be caused by mass lesions that block CSF flow at the interventricular foramen, third ventricle, mesencephalic aqueduct, or lateral apertures [107,125,127-131]. Meningitis may also result in blockage of CSF flow at the lateral apertures [107,132]. Hydrocephalus has been seen in several miscellaneous disorders, including galactosialidosis in a 5 year old Schipperke dog [133], cerebellar degeneration in Bull Mastiff puppies [134,135], neuroaxonal dystrophy in a 9-week-old Jack Russell Terrier [136], primary ciliary dyskinesia in dogs [137-139], hypertrichosis (growth of hair in excess of normal) in Golden Retrievers [140], hereditary cerebellar abiotrophy in Australian Kelpie dogs [141], arachnoid cysts within the quadrigeminal cistern [308], and in a dog presented with continuous tail chasing [142]. Hydrocephalus is thought to play a role in the development of hydrosyringomyelia (see syringomyelia and hydromyelia) in dogs and hypodysplastic hypernatremia in dogs and cats [143,144].

The use of additional classification terms as non-obstructive or communicating hydrocephalus can be confusing and has been challenged in people, in whom increased pressure leading to hydrocephalus is virtually always a result of blockage, whether it is along the pathway of CSF flow or at the site of resorption [75]. Overproduction of CSF in cases of choroid plexus papillomas is considered a rare cause of hydrocephalus in people, and to my knowledge, has yet to be reported in animals. At this time, the form of hydrocephalus in people termed "normal pressure hydrocephalus" which is the result of an imbalance between production and resorption of CSF, usually around the brain convexities, and is seen in late middle-aged and elderly groups, has not been reported in animals. The term "external" hydrocephalus refers to excessive collection of CSF within the subarachnoid space rather than in the ventricular system and is seen in cases of generalized brain atrophy. This form has been reported in a 12 week old Fox Terrier presented with hydrocephalus [304].

On gross inspection the brain may be enlarged with loss of gyral pattern and decreased depth of sulci. In severe cases the

cerebral hemispheres contain extremely large, fluid-filled lateral ventricles, with the cerebral cortex often being reduced to 3 - 4 mm in thickness. The loss of white matter from distension and atrophy is generally more severe than the gray matter loss [106]. The lateral ventricle may extend into the olfactory peduncle and bulb. Pressure from ventricular enlargement may result in atrophy of the corpus callosum, disruption of the septum pellucidum and atrophy of associated structures, including subcortical white matter, optic radiation, internal capsule and auditory radiation. The basal nuclei are usually intact. Blockage of the lateral apertures will result in extensive dilatation of the entire ventricular system. Dilatation of the fourth ventricle may result in marked cerebellar compression along with flattening of the pons and medulla oblongata [106]. Distension of the central canal (hydromyelia) and syrinx formation may also occur in the cervical spinal cord due to the increased intraventricular pressure [145,146]. A developmental stenotic mesencephalic aqueduct is typically associated with fused rostral colliculi [106]. Microscopically, the ependymal lining is frequently disrupted and there may be evidence of forking, gliosis and septum formation. A pronounced subependymal edema is usually present. In one report of acquired hydrocephalus in puppies, there was severe periventricular, choroidal, and meningeal inflammation with fibrinous exudate and neutrophilic and mononuclear cell infiltrates, and multiple false diverticula emanating from the lateral ventricles [120]. Severe meningitis, choroid pleuritis, and ependymitis can occur with feline infectious peritonitis virus [117]. Bleeding is a potential complication of hydrocephalus. Chronic subdural hematomas have been reported in a hydrocephalic 2 month old Newfoundland puppy [307].

Small, toy, and brachycephalic breeds (Maltese, Yorkshire Terrier, English Bulldog, Chihuahua, Lhasa apso, Pomeranian, Toy Poodle, etc.) are at high risk for hydrocephalus. In one study, 53% of 564 hydrocephalic dogs manifested clinical signs by 1 year of age [108]. A distinction between congenital and acquired forms of hydrocephalus may be very difficult from a clinical viewpoint especially since infectious agents may cause hydrocephalus postnatally in young puppies [120]. Furthermore, the confusion in terminology is reflected in the results of one epizootiologic study from 14 veterinary schools in the United States in which 30% of 564 dogs classified as having "hydrocephalus due to congenital origin" were over 2 years of age [108]. Genetic disease has been reported. In Siamese cats, hereditary hydrocephalus is transmitted as an autosomal recessive trait [147]. The congenital hydrocephalus seen in New Zealand Golden Retriever puppies with hypertrichosis appears to have an autosomal mode of inheritance [140].

Clinical examination of newborn and immature hydrocephalic animals typically reveals an enlarged, dome shaped cranium, and open sutures and/or fontanelles that may be bulging in an animal that continuously cries out, has visual and auditory impairment, and altered mental status (ranging from hyperexcitability to severe depression). Other signs may include sporadic seizures, a gait that is uncoordinated, spastic, and clumsy, head tilt, circling, dilated and fixed pupils, and head pressing [148]. Ventrolateral strabismus may occur as a result of encroachment on the orbit from expanding frontal bones, in which case eye movements are normal. Less common signs are positional and spontaneous nystagmus, vomiting, and cervical pain. Some adult Golden Retrievers with hydrocephalus and hypertrichosis manifest behavioral abnormalities (e.g., aggression, hyperactivity, slow learning and other temperament changes) that make them unacceptable pets [140].

Hydrocephalus may be confirmed by radiographic demonstration of enlarged lateral ventricles. Plain radiography will often reveal a ground glass appearance throughout the cranial vault. Cranial sutures and/or open fontanelles may be evident after the normal age for closure and skull ossification. Ultrasonography through open fontanelles [149], CT, or MRI are very useful diagnostic aids [129,150]. Measuring ventricular volume using quantitative MRI also appears to be a useful tool and may help in understanding the relationship between ventricular volume and neurological disease [151]. In one study, a high incidence of asymptomatic (ventricular enlargement or ventriculomegaly) was noted in clinically normal dogs [152], a finding sometimes termed "occult hydrocephalus". Measurement of basilar artery resistance index (a correlate of intracranial pressure) using transcranial doppler ultrasonography, a non-invasive and relatively inexpensive technique, reportedly correlates with neurologic status in dogs with congenital hydrocephalus [296]. Electroencephalographic traces usually have a characteristic pattern of high amplitude (25 - 200 mV), slow wave (1 - 5 Hz) activity, often with a superimposed fast frequency of 10 to 12 Hz. Fundic examination may reveal papilledema. Collection of CSF for analysis is usually not performed since it may precipitate brain herniation due to the presence of increased intracranial pressure.

Prognosis is sometimes related to an underlying disease (such as cerebral neoplasm), but tends to be guarded to poor. Treatment of animals with severe congenital hydrocephalus is futile due to the large amount of tissue destruction and atrophy. Indeed, the efficacy of corticosteroids and surgical shunt procedures in animals with "acquired" hydrocephalus remains uncertain due to the lack of well controlled clinical trials and to incomplete knowledge of the underlying pathogenesis of hydrocephalus. Treatment of the cause of acquired, adult-onset hydrocephalus would seem to be a logical pursuit. Successful surgical shunting procedures have been reported in "acquired" hydrocephalus in both immature and mature dogs [104,153-156]. A ventriculoperitoneal shunt has been used to treat cats with hydrocephalus [157]. Common complications include catheter blockage and sepsis. Dexamethasone, administered at an oral dose of 1 mg divided 4 times daily, for 2 to 3 kg dogs has been used empirically [104]. This dose is gradually reduced over a 2 to 3 week course of therapy. Some animals may be maintained on alternate day dosage schedules. Dexamethasone at 2 - 4 mg/kg has been

suggested for patients with exacerbated/progressive signs [107]. In cats with mild signs, intermittent or short- and long-term corticosteroid usage may be helpful, e.g. prednisone at 1 - 2 mg/kg, sid or bid, PO, along with (or given separately) furosemide at 2 mg/kg bid or tid, PO [105]. Corticosteroids are believed to primarily affect brain bulk and CSF production, not CSF absorption [158]. In humans, acetazolamide, isosorbide, and furosemide can reduce CSF production considerably and may provide short-term benefits [75].

### **Lissencephaly**

Lissencephaly is a rare developmental defect characterized by a small, smooth-appearing cerebrum with rudimentary or no gyri (agyria) or sulci present and derangement of cells of the cerebral cortex. This anomaly has been reported in Lhasa apso dogs, in several breeds of dogs with cerebellar hypoplasia and dysplasia, including Wire-Haired Fox Terriers, Irish Setters, and Samoyeds [65,159,160,309] and in Korat cats with associated microencephaly [106]. Lissencephaly results from disturbance of neuronal migration and proliferation during development. The condition involves only the neocortex, with the hippocampal and olfactory lobes being normal [106,159]. The neocortex is thicker than normal (pachygyria) and contains scattered heterotopic white matter bundles, especially in the thin superficial molecular layer and in the 4th cortical layer. Randomly arranged neurons may be seen in the deeper cortical layers, suggesting arrested migration. In affected Lhasa apso dogs in which the cerebellum was grossly normal, changes were also observed in the flocculonodular lobe of the cerebellum that were characterized by marked heterotopic changes in several folia in which Purkinje cells were irregularly dispersed within the granular layer, the molecular layer was hypercellular and nests of heterotopic glial cells were in the roof nuclei [159].

Clinical signs usually are detected in the first year of life and are characterized by erratic behavior patterns, including episodic aggression, growling at imaginary objects, confusion, depression, hyperactivity, visual deficits, and seizures. Behavior alterations, including self-mutilation, also occur in cats. Gait and posture are usually normal but slight hypermetria may be present when running. Postural reactions tend to be sluggish but normal, although mild proprioceptive deficits have been observed [159]. Spinal reflexes are normal. Bilateral menace deficit may be the only deficit in cranial nerve testing. The observation that neurological abnormalities were mild or delayed in onset after birth suggests the dog is less dependent on the cerebral cortex for sensorimotor function than is man [159]. Abnormal wave tracings are detected electroencephalographically. Neuroimaging studies in animals have demonstrated a smooth cerebral brain surface, as in humans, along with a broad cortex in relation to a narrow white matter layer [75,309].

Prognosis is guarded. Treatment is symptomatic. Seizures may be controlled with anticonvulsant therapy.

Neuronal heterotopia in Lagotto Romagnolo dogs is a recently reported disorder that remains to be classified, although it may be within the spectrum of lissencephalic malformations [298]. Clinical signs began around 7 weeks of age and included tetraparesis with hypermetria, intention tremor, and poor conscious proprioception. Mentation and spinal reflexes are normal. Affected dogs have facial dysmorphism characterized by inferior prognathia and an atypical brachycephalic skull. With time, cerebellar signs progressively improve to apparent clinical normality by 1 year of age. Gross examination of the brain is normal (including normal gyration). Microscopic lesions are characterized by diffuse abnormal neuronal migration and maturation in the cerebral cortex, cerebellum and pons. The abnormal neurons appear monomorphic with vesicular nuclei and basophilic cytoplasm. Similar cells are also present in hemispheric and cerebellar white matter. A genetic disorder is suspected.

### **Meningoencephalocele**

This is a lethal malformation characterized by herniation of part of the brain and meninges through a defect in the skull (cranioschisis or cranium bifidum) [106,109]. The condition may occur spontaneously in animals [161]. It has been seen in kittens following exposure of pregnant cats to a variety of teratogenic agents, including methylmercury, hydroxyurea and griseofulvin [113,162-164], and it occurs in male and female Burmese kittens in which it is inherited as an autosomal recessive trait (the phenotype is impenetrant in at least some homozygote cats) [165,166]. Other related dysraphic anomalies associated with failure of closure of the neural tube include meningocele, exencephaly, anencephaly, and meningomyelocele. In affected animals, the two cerebral hemispheres develop but do not separate from the skin ectoderm that inhibits normal intramembranous ossification from which the calvaria develop. This results in the large skull defect that allows the brain to protrude [106]. Lateral ventricles may be dilated. The cerebrum is often herniated through openings in frontal and parietal bones and may contain a central cavity. Medulla oblongata, midbrain, cerebellum, hypothalamus, and sometimes the thalamus remain in the skull, but are often compressed and distorted. Craniofacial abnormalities in Burmese kittens are characterized by skin-covered masses (encephaloceles) bulging from the top of the head, shortened maxilla, bifid tongue, and absence of eyes, eyelids, and external nares [109,166]. Controlled breeding in Burmese colonies may eliminate the trait; however, a high rate of carriers reportedly exists in the Burmese breed.

### **Myelodysplasia**

Myelodysplasia refers to spinal cord malformation and in humans this developmental disorder may involve several structures including spinal cord, vertebral column, muscles, and skin [167-170]. Myelodysplasia in dogs primarily affects the spinal cord and as such, has been termed "neurospinal dysraphism" [171] or "spinal dysraphism" [172]. This myelodysplastic condition most commonly occurs in Weimaraner dogs [172-175] in which it is transmitted by a codominant lethal gene with reduced penetrance and variable expression [176]. The homozygous condition is lethal. This disorder has also been reported sporadically in other breeds of dogs, including but not limited to Dalmatian, Rottweiler, West Highland White Terrier, German Shepherd, Golden Retriever, and an Alaskan Malamute [177-183] (see also links to other developmental disorders, below). Prenatal studies have shown that dysplastic changes, resulting from abnormal migration of mantle cells, are evident in embryos (24 - 28 days of gestation) obtained by mating severely dysplastic Weimaraner dogs [171,184]. Pathologically, the malformation includes hydromyelia, duplicated, stenotic, or absent central canal, syringomyelia (usually in dorsal columns and often delayed in its formation until dogs are several months old [106,172, 175], chromatolysis and loss of nerve cell bodies in gray matter, disrupted dorsal median septum and ventral median fissure, and gray matter ectopias. In any affected animal, these morphological changes may be present in varying degrees in different cord segments, but occur most commonly in thoracic and upper lumbar spinal cord segments. However, in one prenatal Weimaraner study, major histological differences between normal and dysraphic fetuses were confined to the lumbosacral region of the cord [171,184]. Dysraphic lesions in fetuses included failure of the dura mater to differentiate/separate from the vertebral canal periosteum, absence of the ventral median fissure and fusion of ventral white matter, and gray matter architectural disruption. In some dysraphic fetuses, misplaced gray matter caused marked reduction in size of the central canal. Central canal diverticula were common and the ratio of gray matter diameter to spinal cord diameter was significantly greater in affected fetuses [171,184]. Clinical signs usually appear by 4 to 6 weeks of age; however, abnormal spinal reflexes reportedly are observed in newborn dysplastic puppies. Affected animals have a symmetrical bunny hopping pelvic limb gait, wide based stance, and overextended pelvic limbs with depressed proprioception. Less constant signs include scoliosis, abnormal hair streams in the dorsal neck region, and koilosternia (gutter-like depression of the chest) [172]. Clinical signs neither progress nor regress. There is often a poor correlation between the severity of the clinical signs and the histopathological lesions [174]. Indeed, Summers and colleagues [106] have seen affected Weimaraner puppies without microscopic spinal cord lesions. Routine hematology, radiography and CSF analysis are usually within normal limits. Animals can lead a normal life. There is no treatment.

Note that vertebral anomalies may be associated with myelodysplasia as a result of the close embryonic origin of the spinal cord and vertebral column (i.e. notochord, neural tube, and sclerotomal mesoderm), e.g., malformations of the vertebral bodies and ribs have been reported in a Pekingese dog with spinal dysraphism, along with agenesis of the cauda equina [185]. Similarly, myelodysraphism may be seen with other developmental conditions, such as spinal canal stenosis [45,181], spina bifida, meningoencephalocele, syringomyelia, hydrocephalus, and arachnoid cysts.

### **Occipital Dysplasia**

Occipital dysplasia refers to an abnormally large foramen magnum, resulting from a defect in development of the occipital bone (incomplete ossification of the ventromedial part of the supraoccipital bone [186], has been described in small/medium and toy breed dogs that are often brachycephalic, including Yorkshire Terrier, Pomeranian, Maltese Terrier, Chihuahuas, Pekingese, as well as in Miniature and Toy Poodle, Miniature Keeshond, and Beagle [186-191]. The abnormality, which is readily revealed by frontal radiographs of the skull, consists of a key shaped dorsal midline extension of the foramen magnum into the occipital bone. In one morphometric radiographic study of skulls from 80 Pekingese dogs (75 adult and 5 juvenile), the shape of the foramen varied from ovoid to rectangular and the dorsal notch was observed in all but 2 skulls [192]. Variability in the area of the foramen was mainly correlated with total height of the foramen, including the dorsal notch. The foramen magnum index (the ratio between the maximum width and the total height of the foramen) was not significantly correlated with age, but was significantly larger in female dogs. It was concluded that the large variability in the shape and size of the foramen magnum and the absence of any neurological problems in dogs of this study indicated that the dorsal notch of the foramen magnum in brachycephalic dogs is a normal morphological variation, rather than a pathological condition [192]. This has been confirmed by other studies [186,193]. In another morphometric study involving German Shepherd puppies, occipital dysplasia was not found [194].

The absence of neurological deficits in animals of the above-mentioned studies is consistent with earlier reports of occipital dysplasia being a subclinical (or nonclinical) condition [100,186], and that presence of neurological signs such as ataxia, cervico-occipital pain, personality changes, convulsions, pawing at the side of the face, ear or neck, protrusion of the tongue, and dysphagia in dogs with this malformation reflects some other underlying condition, such as hydrocephalus [195]. A more

recent report suggests that intramedullary CNS abnormalities, such as hydrosyringomyelia, may be present concurrently with occipital dysplasia and should be considered as a possible cause of clinical signs such as cervical hyperesthesia and paresis/tetraparesis [196]. Occipital dysplasia and hydrosyringomyelia are sometimes seen in people with Chiari malformations. Interestingly, some of the signs originally described by Bardens [195], especially the cervical pain and frequent scratching, have been reported in dogs with Chiari I malformation, usually with accompanying hydrosyringomyelia (see Chiari malformations). It has also been suggested that there may be an increased potential for herniation of the cerebellum or brainstem through the enlarged foramen magnum [197], although such prolapse is normally prevented by a fibrous membrane (dura mater and connective tissue) covering the dorsal notch [186,192]. In the report by Bagley and colleagues, this membrane appeared to compress the underlying spinal cord and brainstem in one dog [196].

### **Optic Nerve Hypoplasia**

Optic nerve hypoplasia is an uncommon congenital abnormality of the posterior segment that may be unilateral or bilateral and may be accompanied by microphthalmia or other congenital ocular defects, such as retinal dysplasia, retinal detachment, and sometimes, hydrocephalus. The underlying pathogenesis has not been established. Pathologically, the optic nerve is atrophic with reduced numbers of optic nerve fibers. Vacuolation and paucity of neurons may be observed in ganglion cells of the retina. The optic nerve foramen/canal may be markedly narrowed in some affected animals. Optic nerve hypoplasia is thought to be inherited in Miniature Poodles and has been seen occasionally in several canine breeds, including Beagle, Dachshund, German Shepherd, Miniature Schnauzer, Rough Coated Collie, St. Bernard, Miniature and Toy Poodle, Russian Wolfhound, Tervuren, English Cocker Spaniel, and Great Pyrenees [198-206]. Unilateral optic nerve hypoplasia and hydrocephalus were reported in a 3 year old Pekingese [207]. A possible relationship between small optic nerve heads and optic nerve hypoplasia was described in colony Beagles [208]. Optic nerve dysplasia was reported in American Cocker Spaniels with inherited (probably autosomal recessive) multifocal retinal dysplasia [209]. Congenital blindness associated with multiple ocular anomalies, including optic nerve hypoplasia, has been reported in a family of Bouvier des Flandres (successive litters from the same parents as well as from father x daughter matings were affected) [210]. The diameter of the optic nerve was reportedly reduced in a colony of Dachshunds homozygous for the merle (dappled M) gene [211]. Optic nerve hypoplasia and microphthalmia have also been reported in cats as a sporadic condition [212], in kittens secondary to griseofulvin treatment of the queen during gestation [113], and in association with the inherited craniofacial malformation of Burmese cats [166].

Clinical signs of severe unilateral optic nerve hypoplasia include ipsilateral mydriasis, blindness, menace deficit, and absent direct pupillary reflex, but with a normal consensual reflex in the affected eye following stimulation of the normal eye. Severe bilateral involvement will result in blindness, bilateral mydriasis, absent menace response, and reduced/absent pupillary reflexes.

Diagnosis is suggested by a history of visual impairment from birth. Ophthalmoscopic examination reveals variable reduction in the size of the optic disk with normally appearing retinal vessels. Visual evoked potentials will be absent while ultrasonography may be a useful diagnostic technique [213,214] (also see Electrodiagnostics). Note that electroretinography will be normal since neuroretinal structures (e.g., rods and cones) responsible for generating the electroretinogram are not affected. The pattern evoked response, generated more from ganglion cells than photoreceptors, may also be abnormal (Dr. J.E. Steiss, Tuskegee University, personal communication, 2002). Prognosis is poor. There is no treatment.

Optic nerve aplasia is a very rare congenital anomaly characterized by absence of optic nerve, optic disk and retinal vessels. Interestingly, the size of the optic nerves, density of axons, and total number of axons were not affected in the autosomal recessive mutation carried in a family of achiasmatic (lacking an optic chiasm) black Belgian sheep dogs [106,215]. In these dogs each optic nerve was continued by an ipsilateral optic tract. Affected dogs had a congenital rapid pendular nystagmus with unimpaired vision.

### **Osteochondromatosis**

Osteochondromatosis is a relatively uncommon clinical disease entity in dogs and, especially, in cats (based on few reported cases in cats) in which multiple cartilage-capped, partially ossified protuberances or exostoses arise (usually near metaphyseal growth plates) from the cortex of bones of endochondral origin [45,216-222]. Synonyms for osteochondromatosis include multiple cartilaginous exostoses, hereditary multiple exostoses, multiple osteochondromatosis, diaphyseal aclasis, dyschondroplasia, and hereditary deforming chondrodysplasia [223]. Osteochondromatosis implies involvement of several bones (polyostotic), although single bone involvement (monostotic) may be seen, in which case the term chondroma has been used, indicating that the growths are benign tumors. However, osteochondromas are not true chondromas but developmental disturbances since their growth is controlled by growth hormone and cease enlargement at time of growth plate closure and are, therefore, unlike true tumors that demonstrate uncontrolled growth (Dr. R. Pool, Mississippi State University, personal communication, 2001). The cartilage-cap portion of osteochondromas undergo endochondral ossification with subsequent replacement of much of their central mass by bone, so that eventually the cortical

surfaces of the parent bone and the developing bony stalk are continuous and have confluent marrow spaces [223]. Although canine osteochondromas are a developmental, chondrodysplastic anomaly [223], for purposes of differential diagnosis they are also included as one of several primary skeletal tumors (see spinal cord tumors).

The etiology of canine osteochondromas is uncertain. They may arise directly from growth plate cartilage as a result of a defect in the perichondrial ring, from physical stresses causing proliferative responses at the margin of the physis, or from some form of periosteal disturbance that induces perichondrial growth. Any bone of endochondral origin may be affected; however, in decreasing frequency, vertebrae (especially spinous processes, but also body and arch), ribs, long bones, feet and pelvis are most often involved in dogs [223]. Bones of intramembranous origin (i.e., calvarium and facial bones) are not affected in dogs. Growth of osteochondromas in dogs typically ceases at the time of skeletal maturation, although occasionally, some may progress after skeletal maturity [224]. While a familial or genetic etiology is suspected [223,225], there is no apparent breed or sex predisposition, although several reports involve Alaskan Malamutes, and in one study, seven of the eight affected dogs had mixed Terrier breeding [221].

Osteochondromatosis is frequently a subclinical condition diagnosed as an incidental radiographic finding. However, neurological signs occasionally occur in animals associated with spinal cord compression secondary to vertebral osteochondromas in any region of the spinal column, but most commonly cervical and/or thoracic areas [219,224, 226,227]. Signs observed will depend on the location of the masses (e.g., cervical syndrome, cervicothoracic syndrome, and thoracolumbar syndrome).

There may be variable signs of pain on palpation of the thoracic or cervical spine. Onset of neurological signs typically occurs prior to 1 year of age, although osteochondromatosis may be first diagnosed in older dogs (see also, malignant transformation, below). Osteochondromatosis may involve other tissues such as synovial joints, and tracheal rings.

Concurrent skeletal and tracheal osteochondromatosis has been observed in a young Alaskan Malamute [226].

Diagnosis may be made using survey radiography but evidence of cord compression will require myelography and/or imaging [311]. Radiographically, osteochondromas usually appear as large, smoothly contoured cystic bony masses, with irregular or well-delineated borders, sometimes with mottled patterns of radiolucency and radiodensity [223,224]. Fusion of vertebrae at articular facets in the presence of normal intervertebral disks, may be observed [224]. Microscopic examination of a biopsy specimen, which includes the cartilage cap and bony stalk covered by a membrane continuous with the periosteum, will confirm the diagnosis [223]. During active growth, the cartilage resembles a physis with typical endochondral ossification present. The cartilage cap may be incomplete or absent in mature lesions. Osteochondromas may also be characterized using special imaging techniques, such as CT [227].

Surgical excision (including removal of the perichondrial membrane on the surface of the cartilage cap), spinal cord decompression, and perhaps vertebral stabilization, are necessary in animals with clinical evidence of spinal cord attenuation.

While post-operative vertebral fracture has been reported [228], there are several reports of successful surgical outcomes [226,227,229]. Surgical removal may be easier when osteochondromas are less well developed, at which time they are softer and poorly vascular, since within a few months, the cancellous bone becomes harder and much more vascular [226].

Recurrences may occur. Prognosis is guarded, especially in young animals with osteochondromas involving multiple vertebral sites where subclinical masses may assume importance as they grow until the skeleton matures. Early surgical removal may eliminate development of clinical complications. Furthermore, there is evidence that osteochondromas may undergo malignant transformation to chondrosarcoma and osteosarcoma in older dogs, frequently between 7 and 10 years of age [224](7), with potential for metastasis [221,230,231]. Thus, early removal will also remove this latent threat of malignancy. Breeding of affected dogs should be discouraged because of the occurrence of osteochondromas in 2 dogs from a litter of 5 sired by a dog that also had the condition [225]. Recently, malignant transformation of solitary spinal osteochondroma to an osteosarcoma was reported in 2 mature dogs [232].

Osteochondromatosis in cats differs significantly from the condition in dogs. The osteochondromas typically first appear in the skeletons of mature cats (e.g., from 2 to 4 years of age), growth of the bony mass is progressive, and the lesions show microscopic transformation from hyperplasia to characteristics of virus-induced parosteal sarcomas [223]. Virus particles have been identified ultrastructurally from feline osteochondromas and are morphologically identical to feline leukemia virus [233]. Other viruses suggested are feline fibrosarcoma virus or another member of the feline retrovirus family [223]. Any bone can be affected in cats, including the flat bones of the skull. Most common sites, in decreasing frequency, are rib cage, scapulae, vertebrae, skull and pelvis [223]. Osteochondromatosis in cats has no breed or sex predisposition or hereditary pattern. Prognosis is grave for any affected cat. Some tumors undergo transformation into osteosarcoma and chondrosarcoma and no cat has lived longer than a year after onset of clinical signs [223].

There are sporadic reports of a focal cartilaginous lesion, termed solitary cartilaginous exostosis, resulting in spinal cord compression [25,234]. Young and mature, large-breed dogs (4 month old Rottweiler, 5 month old Bernese Mountain dog, 3.5 month old St. Bernard, and a 3.5 year old Bernese Mountain dog) were affected and the mass in each dog occurred between the dorsal arch of the atlas and the spinous process of the axis. Radiographically, the masses were partially calcified, seemed to arise from the dorsal arch of the atlas or from the dorsoatlantoaxial ligaments and extended into the vertebral canal [25]. In

some cases, the dorsal arch of the atlas was irregular or thickened with erosion and shortening of the pedicles and spinous process. Histologically, the masses were composed of a fibrocartilaginous matrix, but without bone formation. Surgical removal of the mass in one dog resulted in a complete recovery [234]. At this time, these focal cartilaginous lesions remain difficult to classify. They seem to be radiographically similar to calcinosis circumscripta/tumoral calcinosis (CC-TC) [235], a possible metabolic disorder [236] having an apparent predilection for the atlantoaxial articulation. However, CC-TC is histopathologically different from osteochondroma and cartilaginous exostosis (Dr. R. Pool, Mississippi State University, personal communication, 2001). A lesion of CC-TC consists of a radiodense aggregation formed of multiple loculi of amorphous calcareous deposits located in periarticular soft tissue. The calcium deposits are bordered by macrophages and giant cells and are encapsulated by fibrous tissue septa of variable thickness that may rarely contain foci of metaplastic cartilage and bone tissue [237].

### **Sacrocaudal Dysgenesis**

Congenital malformations of the sacrocaudal (sacroccygeal) spinal cord and vertebrae have been well described in tailless Manx cats, in which the disease is transmitted as an autosomal dominant trait [238-241]. This disease is also known as 'caudal dysgenesis' and exemplifies a malformation brought about by breeders selecting for tailless cats. The disorder is associated with varying degrees of agenesis/aplasia (absence of formation) or dysgenesis/dysplasia (defective development) of caudal lumbar, sacral and caudal (coccygeal) vertebrae, and spina bifida. The variable expression of Manx taillessness is a salient and consistent feature of the Manx syndrome [242]. Pathologically, subcutaneous cyst formation, meningocele, meningomyelocele, shortening of the spinal cord and absence of cauda equina, and myelodysplasia of the caudal lumbar, sacral, and caudal spinal cord segments including central canal defects, syringomyelia, myeloschisis (cleft within spinal cord) and abnormal gray matter differentiation have been described in affected animals [106,240, 243,244].

Clinical signs in seriously affected cats may be progressive after birth, perhaps associated with progressive syringomyelia [14], or they may remain static in cats with a partial disability. Neurological signs include plantigrade posture, hopping gait, pelvic limb paresis/paraplegia, fecal and urinary incontinence, and perianal sensory loss. Urodynamic studies have shown significant abnormalities of vesiculourethral function: detrusor areflexia, autonomous pressure response to bladder filling, a dysfunctional proximal urethra, and poor quality pelvic floor electromyographic activity [245]. Catecholaminergic histochemical studies of the bladder and urethra have demonstrated complete absence of adrenergic fibers, including the trigone area [245]. Myelography or MRI may outline the meningocele or meningomyelocele, if present.

Prognosis is guarded. There is no treatment. Mildly affected animals may attain longevity if fecal and urinary incontinence are managed. Sacroccygeal dysgenesis may be seen sporadically in other breeds of cats and in dogs [246], the English Bulldog in particular [247].

### **Spina Bifida**

Spina bifida is a developmental anomaly characterized by the presence of a midline cleft in the vertebral arch of a single or several vertebrae. The cleft may involve most of the vertebral arch or only the dorsal spinous process. This anomaly results from failure of fusion of the halves of the dorsal spinous processes and may be accompanied by protrusion of the spinal cord or its membranes. Spina bifida manifesta, cystica, and aperta are synonymous subclassifications indicating presence of meningocele cyst (protrusion of the spinal cord membranes through a defect in the spinal column), myelocele (protrusion of the spinal cord) or meningomyelocele (protrusion of the spinal cord and its membranes through a defect in the spinal column) [247]. Rarely, rachischisis (embryonic failure of fusion of the vertebral arches and neural tube) and myeloschisis (cleft spinal cord resulting from failure of the neural folds to close normally in the formation of the neural tube) are reported together [248]. Spina bifida occulta is characterized by a bony defect without visible protrusion of enclosed vertebral canal structures and is usually associated with smaller defects in the lamina. Most meningoceles and meningomyeloceles occur in the lumbosacral area and mainly involve nerve roots and spinal nerves of the cauda equina rather than spinal cord itself [106]. In such conditions, the meninges and their associated subarachnoid space extend through the vertebral defect to attach to the overlying skin from which CSF may leak. Subdermal or epaxial accumulation of CSF may also be found. As a consequence of the meningeal attachment in the meningomyelocele, abnormal tension may be exerted on the spinal cord. This has been termed tethered cord syndrome [106,249]. The degree of spinal cord dysfunction in tethered cord syndrome appears to be related to both the force and duration of traction [250]. Other anomalies, such as hydrocephalus, multiple thoracic and/or sacral hemivertebrae, may also be present in affected animals [45,247,251,252].

Myelodysplasia, especially in sacrocaudal and lower lumbar segments, consisting of gliosis, hydromyelia (dilation of the central canal), syringomyelia (cavitations within the spinal cord), myeloschisis, or abnormal position of the central gray matter and anomalies of dorsal and ventral horns, may occur with spina bifida. In some instances of myelodysplasia, necrosis of dorsal horns and dorsal white columns has been observed, creating a spongiform appearance to the parenchyma.

Astrocytosis may be seen in affected white matter [253].

The embryonic pathogenesis of this anomaly is controversial: it may represent overgrowth of cells of the dorsal neural tube



that, in turn, interferes with fusion of the neural tube and vertebral arches; or the vertebral arches may fail to fuse as a result of a neuroschistic bleb [247]. Developmental arrest and hydrodynamic theories have also been suggested [45]. Spina bifida (involving cervical vertebrae C1 to C4) was found among multiple congenital malformations in kittens of cats treated during gestation with griseofulvin [113]. Spina bifida/meningomyelocele has also been observed in kittens following methylmercury and ethylenethiourea toxicity studies in pregnant queens [163,254].

While spina bifida has been reported in a wide variety of dogs and cats [253,255-258], there is a high incidence of this condition in young English Bulldogs [247,253] and in Manx cats with sacrocaudal dysgenesis. Spina bifida may occur anywhere along the spinal column but is most common in the lumbar region. In some instances, the defect can be extensive, involving most of the thoracic, lumbar, and caudal vertebrae [257]. Spina bifida is often a subclinical condition and an incidental radiographic finding [259]. Clinical signs in animals with spina bifida usually indicate an associated myelodysplasia or protrusion of the meninges, spinal cord or cauda equina and are usually noticed when affected animals begin to ambulate. Signs may include pelvic limb ataxia and paresis, fecal and urinary incontinence, perineal analgesia, and flaccid anal sphincter [247,252,260]. The analgesia may extend to the most proximal part of the posterior surface of the thighs, to the level of the scrotum and prepuce anteriorly, in male dogs, and to the tail caudally. The site of the bony defect may be marked by dimpling of the overlying skin, streaming of hair coat, and palpable cavitation in the dorsal spinous process. Meningocele alone can be present without neurological deficits [255,261]. Decreased serum and CSF chloride concentrations were documented in a 5 year old Manx cat with spina bifida associated with chloride loss through a fistulated meningocele [261]. In an 8 month old Manx-type cat with neurological deficits and CSF draining from a skin mass dorsocaudal to the sacrum, exploratory surgery and histopathology confirmed a tethered spinal cord and an intradural lumbosacral lipoma associated with a meningocele [262].

Plain radiographs will demonstrate abnormalities ranging from non-fusion of dorsal laminae to a cleft spinous process; however, myelography or advanced imaging techniques (e.g., ultrasonography, CT, or MRI) may demonstrate protrusion of spinal cord, nerve roots, and/or meninges through the sacral defect to the skin or subcutaneous spaces [251,262,263].

Prognosis is guarded to poor, particularly when myelodysplasia is present. In some animals with a fistulated meningocele/meningomyelocele, surgical ligation of the meningocele tract can correct problems associated with loss of CSF [261,262] and surgical untethering may reverse some of the neurological dysfunction caused by the tethered cord syndrome and prevent further deterioration of the motor, sensory and urinary functions [251,262,264].

### **Syringomyelia and Hydromyelia**

Congenital syringomyelia (cavitation of the spinal cord parenchyma) and hydromyelia (dilatation of the central canal within the spinal cord) are relatively uncommon malformations of the spinal cord that result from incomplete closure or development of the neural tube [259]. They may occur in isolation or together (hydrosyringomyelia) and may be localized to a short segment of the spinal cord or along great distances. These conditions are most often seen as primary developmental defects in association with congenital conditions such as myelodysplasia [182,185], spina bifida, sacrocaudal dysgenesis, meningocele, and other CNS malformations such as hydrocephalus, Chiari malformations [44,78], occipital dysplasia [196], and Dandy-Walker syndrome [76]. Since it is often impossible to differentiate syringomyelia and hydromyelia using imaging techniques [76], I have used the combined term hydrosyringomyelia frequently in this review in line with human nomenclature, although some authors prefer the term "syringohydromyelia". The pathogenesis of primary hydrosyringomyelia is uncertain. It may be a hydrodynamic compensatory lesion that occurs in some animals with hydrocephalus and increased intraventricular pressure, especially where there is an obstruction of CSF circulation through the lateral apertures of the fourth ventricle [106,107,265]. Experimental syringomyelia has been induced in dogs with cisternal kaolin injection [266]. The dogs had arachnoiditis, hydrocephalus, and syringomyelia that communicated with the fourth ventricle. In a dog with spontaneous disease, partial obstruction to CSF was found associated with cervical cord pachymeningeal fibrosis [79]. Dynamic changes in cervical spinal cord intramedullary pressure with the neck in the flexed position have been postulated to play an important role in syrinx growth in experimental studies using dogs [267]. Hydrosyringomyelia may also occur secondary to edema of neoplasms, spinal cord trauma, vascular compromise, or inflammation [79,106,268]. Cervical hydrosyringomyelia with communication to the 4th ventricle has been observed in a dog with a nerve sheath tumor involving a C6 nerve root [269]. A rare vascular malformation primarily involving thick-walled veins was causally implicated in an 8.5 year old Lhasa apso dog with hydrosyringomyelia (the condition in this dog was considered similar to Foix-Alajouanine syndrome in people, an angiodysgenetic necrotizing myelopathy) [146]. Obstructive hydrocephalus and malformations of the cerebellar vermis and hypoplasia of the roof of the fourth ventricle were also present. Hydrosyringomyelia has also been described as an idiopathic condition in absence of a primary or developmental cause [79,106,270].

Syringomyelia is considered to result from a rupture of the ependymal lining of a dilated central canal with dissection of adjacent spinal cord parenchyma or is the result of edema collecting in the dorsal funiculi secondary to the hydromyelia

[106]. The syrinx is often found in the center of the dorsal funiculi and may expand into the median areas of the dorsal gray columns [106]. In many cases, a communication between the syrinx and the dilated central canal is not apparent. Accordingly, syringomyelia may be communicating or non-communicating. The cavity may be glial-lined (e.g., by astrocytes) but is not lined by ependymal cells. Syringohydromyelia is often prominent in the cervical cord and may communicate with the fourth ventricle [76,196,271], but also may occur in thoracic and lumbar spinal cord segments [78,106]. It is possible that the syrinx may progressively expand, especially through planes of structural weakness, such as the gray matter of the dorsal horns [79,106], leading to progressive clinical signs [14,78,79]. Neuronal necrosis and chromatolysis, edema and variable fibrillary astrocytosis in gray matter, and presence of spheroids and swollen axonal sheaths have been reported in dogs with hydrosyringomyelia [79,106].

Affected animals of various breeds (not including Weimaraners with myelodysplasia) range in age from 12 weeks to 12 years. Clinical signs are variable depending on the location and severity of the hydrosyringomyelia as well as presence or absence of other congenital CNS malformations. Cervical syringomyelia, with or without hydromyelia, has been reported in several immature and mature dogs in conjunction with signs of paraparesis, tetraparesis, scoliosis, torticollis, or cervical pain [78,79,145,182,196,269,271,272]. Signs of a central canal spinal cord lesion extending to cervicothoracic cord segments may include dermatomal paresthesia over the shoulder or neck, leading to persistent intense scratching at the shoulder or flank region, muscle atrophy of cervical epaxial muscles and/or thoracic limb muscles, weakness, especially in thoracic limbs, and decreased spinal reflexes [77,78]. A direct causal relationship between scoliosis and hydrosyringomyelia has been suggested via progressive destruction of gray matter by the cavitation resulting in denervation and atrophy of epaxial muscles unilaterally [78,79,107,145]. Mild dysphagia has been reported in one affected dog [271]. Progressive paresis, paraparesis and pelvic limb proprioceptive deficits were reported in an 11 year old Fox Terrier dog with what was believed to be an acquired syringomyelia localized in upper lumbar cord levels [270]. Onset of signs may be peracute [269] or insidiously progressive over several weeks, months or years [79,271]. Weimaraners with myelodysplasia typically do not show progressive clinical signs. Cervicothoracic syringomyelia and myelodysplasia (including thoracolumbar cord hypoplasia), but without hydrocephalus, was observed in a 5 month old West Highland White Terrier puppy with urinary and fecal incontinence, bunny-hopping pelvic limb gait, and mild scoliosis of the thoracolumbar spine [182]. Syringomyelia has also been identified in animals with arachnoid cysts [8].

CSF analysis is usually normal in animals with hydrosyringomyelia; however, it should be noted that a CSF tap led to respiratory arrest and death in one affected dog [79]. Electromyography may reveal abnormal spontaneous potentials in cervical epaxial or thoracic limb muscles (with cervical hydrosyringomyelia). In some cases, myelography has revealed diffuse spinal cord enlargement [76,145,270,272] and presence of contrast agent within the central canal (canalogram) [76,79,272]. In other cases, myelography has been negative. Imaging techniques such as CT and MRI may help outline the extent and location of the lesions [8,76,196 269-271]. The latter is considered better for defining intraparenchymal spinal cord abnormalities [196,269,273].

The exact nature of the hydrosyringomyelia and its variable progressive or non-progressive course, as well as possible presence of other congenital CNS malformations, make prognosis difficult to assess. At this stage of our knowledge, prognosis is probably guarded, at best. However, successful medical, e.g., long-term prednisolone and furosemide [8,272] or surgical treatment, including syringotomy [270] and drainage [196] have been reported. Hydrocephalus and cervical/thoracic syringomyelia in 3 month old Japanese cat appeared to resolve following establishment of a ventriculoperitoneal shunt [305].

### **Vertebral Anomalies**

A wide variety of congenital developmental abnormalities of the spinal column can occur in animals, but the majority, at least in dogs, are minor and cause no clinical signs [274]. Vertebral anomalies often result from disruption of normal development and regression of the embryonic notochord, segmentation of mesoderm into somites, or vascularization and ossification of the vertebrae [45,259]. The term "complex congenital vertebral anomalies" denotes the presence of several vertebral malformations occurring in an animal.

Hemivertebra - Is a malformation that may be the result of hemimetameric displacement of somites, resulting in right and left hemivertebrae, or it may result from altered vascularization and ossification of vertebrae. While the majority of cases do not produce any obvious clinical signs, hemivertebra is more often associated with neurological deficits than any other congenital vertebral anomaly. Affected animals are usually less than one year of age [275-277]. Neurological signs may result from:

- a. Progressive, severe angulation of the spine, e.g., kyphosis (associated with dorsal hemivertebra), lordosis (ventral hemivertebra), or scoliosis (most often associated with lateral hemivertebra);
- b. Narrowing of the spinal canal (spinal stenosis);
- c. Instability of the involved segments ultimately producing spinal cord compression;

- d. Vertebral luxation or fracture at the site of hemivertebra following a sudden jump, fall or trauma.

The spinal curvatures depend on the number of involved vertebrae and degree of individual vertebral deformity [197]. The breeds of dogs that have been reported to be most commonly affected are the "screw-tailed" breeds: English Bulldog, French Bulldog, Pug, Pekingese, and Boston Terrier (the kinked tail is itself due to hemivertebrae in the coccygeal region). Thoracic hemivertebra was present in a 3 month old English Bull dog with tethered cord syndrome, spina bifida and myeloschisis, and hydrocephalus [251]. The condition has also been seen sporadically in other breeds, e.g., West Highland White Terriers, Fox Terriers, and Yorkshire Terriers. Vertebrae most commonly affected are in the region T7 to T9. Hemivertebra has also been reported in dogs (Rottweiler and Pekingese) with spinal cord dysraphism [181,185] (see myelodysplasia) and in a 4 year old Beagle with an associated arachnoid cyst [2]. Hemivertebra of the 2nd and 3rd lumbar vertebrae was present in an 8 week old Rottweiler puppy with associated scoliosis and syringomyelia of the 2nd lumbar spinal cord segment [278].

Clinical signs may include varying degrees of pelvic limb paresis and paralysis, muscle atrophy, pain on palpation of the spinal column, and often fecal and urinary incontinence. Radiographs show an obvious abnormality of the spinal column affecting a single, or in some cases, several vertebrae. There is usually a marked dorsal deviation of the thoracic or lumbar vertebral column with one or more wedge-shaped vertebral bodies. Disk spaces are usually well preserved. The vertebral end plates are smooth and of normal thickness. Missing vertebrae may be detected [277]. Myelography will often outline compression of the subarachnoid space over one or more of the anomalous vertebrae. Thoracic hemivertebra has been reported as an autosomal recessive disorder in some lines of German Shorthair Pointers [279] and has been associated with rapidly developing flaccid paraplegia in puppies about 6 weeks of age. In these dogs, hemivertebra was found at T4, along with kyphosis (from T3 to T5), incomplete development of end-plates at the caudal aspect of T3 and cranial aspect of T4, and misshapen dorsal spinal processes in this region. Necropsy revealed narrowing of the vertebral canal and compression of the spinal cord adjacent to T3, T4, and T5 vertebrae in each of the affected puppies. The parents were clinically normal and had no phenotype characteristic of the carrier state. An association between vertebral anomalies, including hemivertebra, and neonatal mortality has been noted in Bulldogs [276]. Note that dogs with hemivertebra often have other vertebral malformations, such as transitional vertebrae (see below) [258].

Diagnosis of clinically significant hemivertebrae is based on age, breed, clinical history, clinical signs, radiography, myelography, or specialized imaging techniques. In one radiographic study in Pugs, interpretation of findings was difficult, especially in the thoracic spine due to the massive thorax and the sternum superimposing on the spine [258]. Dogs may be treated with surgical decompression, vertebral realignment and stabilization.

Block Vertebrae - May involve vertebral bodies, arches, or the entire vertebra in any spinal region, and result from disturbed somite segmentation [259]. Partial blocking may occur along with incomplete intervertebral disk development. While abnormal spinal angulation can occur, block vertebrae tend to be stable and be clinically insignificant. Block vertebrae might be confused with traumatic intervertebral disk protrusion or with fused vertebrae following diskospondylitis, vertebral neoplasia, or vertebral fracture-luxation [197], although reactive bone associated with these processes is not present in block vertebrae [45]. The presence of both block vertebrae and hemivertebrae were reported in a 12 week old Rottweiler with clinical and radiographic features of severe cervical scoliosis and mild kyphosis [280]. Apart from pain when head and neck were manipulated, no other neurological deficits were observed. Radiographs revealed a misshapen and foreshortened C6 vertebra, while C3, C4 and C5 vertebrae were largely fused to each other from the caudal aspect of the axis. There was marked left-right asymmetry, normal disc spaces and articular processes were not recognized, and dorsal spinous processes were considerably shortened. The vertebral canal did not appear to be severely compromised. Block vertebrae may occasionally be associated with a stenotic vertebral canal [45] and have been observed in a 7 month old dog with an intracranial arachnoid cyst [281]. Vertebral canal stenosis was noted at the C3 vertebral level in a 5 month old Afghan Hound presented with pronounced cervical kyphosis and moderate cervical scoliosis [282]. The vertebral defects were associated with a reduction in length and diameter of the body of C3, aplasia of the facets between C2 and C3 vertebrae, dorsal arching of C3, duplication of the dorsal spine of C3, and rotation of C1 and C2 about their long axis. No neurological deficits were identified.

Butterfly Vertebra - Results from persistence of the notochord or sagittal cleavage of notochord producing a sagittal cleft of the vertebral body that extends through the body dorsoventrally. The cranial and caudal vertebral end-plates are funnel shaped and this produces a butterfly effect when viewing a dorsoventral radiograph [259]. Butterfly vertebrae are most often detected in brachycephalic, screw-tailed breeds. This anomaly is rarely clinically significant.

Spina bifida - is a developmental vertebral anomaly characterized by the presence of a midline cleft in the vertebral arch of a single or several vertebrae. The cleft may involve most of the vertebral arch or only the dorsal spinous process. It is often an incidental finding but sometimes severe neurological signs ensue with involvement of the spinal cord or cauda equina. There

is a high incidence of spina bifida in young English Bulldogs and in Manx cats with sacrocaudal dysgenesis.

Transitional Vertebrae - Are abnormal vertebrae occurring at cervicothoracic, thoracolumbar, lumbosacral or sacrocaudal junctions that possess characteristics of other vertebral spinal regions, e.g. a rib present on the transverse process of C7 or a transverse process present on the first sacral vertebra [197]. Only the transitional lumbosacral vertebral anomalies appear to be clinically significant, presumably by affecting the size, shape, and plane of the vertebral body, vertebral canal, and intervertebral disk [14,197,283]. Transitional lumbosacral vertebral anomalies are considered to be inherited in German Shepherd dogs and a possible cause of cauda equina syndrome associated with degenerative lumbosacral stenosis [284,285]. The anomaly is characterized by separation of the first sacral segment, identified on the lateral view by the presence of a radiolucent disc space between what are normally the first and second sacral segments. On the ventrodorsal view, the anomaly is characterized by separation of the spinous processes between what are normally the first and second sacral segments. It is hypothesized that in the presence of the transitional segment, the sacroiliac joint at the level of the anomaly is weakened leading to instability, spinal canal stenosis and intervertebral disk degeneration [284]. Lumbosacral transitional vertebra has also been reported in a 3 month old Chihuahua puppy with thoracic limb malformations but without neurological signs [286]. Transitional vertebrae were also one of several subclinical CT abnormalities found in the lumbosacral spine of older large-breed dogs [287].

Scoliosis - As mentioned above, may develop in animals with hemivertebra. It also occurs in cats with hypervitaminosis A. The important association between developmental anomalies of the spinal cord, including Weimaraners with spinal dysraphism/myelodysplasia, and vertebral anomalies such as scoliosis has been previously noted [172,288]. In particular, there are increasing reports of scoliosis occurring in animals with congenital or acquired cystic lesions involving the spinal cord, especially with cervical hydrosyringomyelia (see syringomyelia and hydromyelia), in which the spinal curvature often presents clinically as torticollis [78,79,145,271]. A direct causal relationship between scoliosis and hydrosyringomyelia has been suggested via progressive destruction of gray matter by the hydrosyringomyelic cavitation resulting in denervation and atrophy of epaxial muscles unilaterally, followed by asymmetrical lateral muscle tension and subsequent vertebral deviation [78,79,145]. Unilateral epaxial cervical muscle spasms may also play a role in the scoliosis [145]. Because of this relationship, it has been suggested that the observation of scoliosis and cervical pain in an animal may be the first clinical sign of hydrosyringomyelia [145]. Mid-lumbar scoliosis and mild kyphosis has also been reported in a dog with an arachnoid cyst at T11 - T13 vertebral levels [18]. The focal point of the scoliosis was at L1 - L2. Denervation atrophy was present in the paraspinal epaxial muscles at this level, presumably secondary to the cyst. The cranial endplate of L1 and the articular facets of L1 - L2 were malformed. Thoracolumbar scoliosis has been reported in association with severe myelodysplastic hypoplasia of the thoracolumbar spinal cord in a 5 month old West Highland White Terrier, with accompanying cervicothoracic cord hydrosyringomyelia [182]. The scoliosis in this case may have been the result of asymmetric denervation atrophy of the paravertebral muscles associated with the localized myelodysplasia in the caudal thoracic cord segments.

Stenosis of the Vertebral Canal - May occur with congenital vertebral anomalies, especially in animals with hemivertebrae and block vertebrae (see above), and may be focal, segmental or generalized throughout the vertebral column [45]. A segmental stenosis in the cranial thoracic spine (T3 - T6) of Doberman Pinschers (mainly mature but occasionally, immature dogs) has been reported, sometimes in association with mild lordosis and kyphosis, but usually without clinical spinal cord compression [45]. Most of these cases were incidental findings in dogs being investigated for cervical spondylomyelopathy (Dr. C.S. Bailey, University of California, Davis, personal communication, 2001), a condition in which stenosis of the cervical vertebral canal seems to be a developmental anomaly. Focal vertebral canal stenosis due to malformation of the vertebral lamina of T12 and cranial portion of T13, with associated spinal cord compression and progressive hindlimb paresis, has been reported in a 3 month old Basset Hound [289]. Myelographic studies may help confirm focal vertebral stenosis in animals with signs commensurate with spinal cord compression [45,289,290]; however note that not all animals with vertebral anomalies have spinal cord compression at the site of spinal deformity [290]. Routine decompressive surgery is indicated in cases with clinical signs of spinal cord compression [45,290]. Lumbosacral stenosis of the vertebral canal is sometimes seen in young animals as a developmental anomaly [291]. Cervical stenosis may be seen in developmental malformations of the axis and/or atlas resulting in instability of the atlantoaxial joint and potential attenuation of the upper cervical spinal cord (see atlantoaxial subluxation). Some animals with odontoid process malformations also have a malformed atlas or occipital dysplasia.

Miscellaneous Developmental Disorders - Caudal vertebral malformations occur in Scottish Fold cats (immature and mature) with short, thick, inflexible tails, including shortened vertebrae with enlarged bony vertebral endplates, reduced vertebral spaces and new bone formation tending towards ankylosis of adjacent vertebrae [292]. This osteochondrodysplastic condition

appears to be inherited as an autosomal recessive trait. Signs of pain and gait abnormalities are typically orthopedic rather than neurological. A monolateral hippocampal cortical hamartia characterized by pyramidal cells arranged in a gyrus-like pattern and intermingled with gemistocytic and fibrillary astrocytes was an incidental finding in a 4 year old Pekingese dog with encephalitis [310].

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## Degenerative and Compressive Structural Disorders (29-Jan-2003)

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In this chapter we will review a variety of neurological disorders that result from abnormalities of bones, ligaments, and other mesenchymal tissue that compress the nervous system. Most of these conditions are degenerative in nature, although some represent developmental disorders. The spinal cord and occasionally nerve roots are the nervous tissues most commonly compressed. One condition, disk disease, represents the most common cause of spinal cord compression in dogs.

An outline of this chapter is as follows:

- Calcinosis Circumscripta/tumoral Calcinosis
- Cervical Spondylomyelopathy
- Disk Disease
- Diskospondylitis
- Dural Ossification
- Lumbosacral Stenosis
- Spinal Synovial Cysts
- Spondylosis Deformans
- Miscellaneous Disorders

### **Calcinosis Circumscripta/tumoral Calcinosis**

Focal nodular aggregations of ectopic calcification occurring in the soft tissues have been referred to by several synonyms that include calcinosis circumscripta, apocrine cystic calcinosis, tumoral lipocalcinosis, lipocalcinosis, calcium gout and tumoral calcinosis. In man [1,2] the term calcinosis circumscripta is used to distinguish between those generally smaller nodular calcareous lesions occurring in the skin, subcutaneous sites and skeletal muscle and those histologically similar but often larger multinodular lesions of tumoral calcinosis occurring in the deep peri-articular sites, i.e. soft tissues located adjacent to joints. This nomenclature is beginning to be more commonly accepted to describe similar distribution patterns of nodular deposits of ectopic calcification in animals [3-5].

In the veterinary literature calcinosis circumscripta and tumoral calcinosis have been used as synonyms to describe histologically similar idiopathic conditions characterized by the formation of circumscribed single or multiple nodular masses due to deposition of calcineous material, located either in periarticular connective tissue or in cutaneous tissues over pressure points and bony prominences, in footpads, or in the mouth [6-11]. Etiology and pathogenesis remain obscure. Most reports involve dogs, but the condition has occasionally been seen in cats [12]. Concurrent illness is usually not associated with the different patterns of nodular ectopic mineralization in animals; however, some animals may have underlying renal disease [4-6,13,14]. The prevalence of the condition in young large-breed dogs, particularly German Shepherds, Great Danes and Vizslas, suggests possible hereditary predilection. Calcinosis circumscripta has occasionally been seen following surgical procedures, use of polydioxanone suture material, and progestin (medroxyprogesterone acetate) injections in dogs and cats [15-19]. Calcinosis circumscripta-like lesions have also been reported in dogs associated with the use of choke chains [20]. The pattern of deposition referred to as tumoral calcinosis usually does not directly involve bones or joints [4,8,11]. Clinical signs include one or more hard or fluctuant, spherical, well-circumscribed, non-painful subcutaneous masses [8]. When incised, the masses discharge a chalk-like material. Histopathologically, the masses are characterized by lobular areas of mineralization and degeneration in a fibrous, collagenous matrix with large foamy macrophages, giant cells, lymphocytes, and neutrophils. Some calcific foci are embedded by osseous tissue [4,8]. The mineralized material stains positively for calcium, phosphorus, carbonates and hydroxyapatite crystals. The ground substance stains positive for acid mucopolysaccharides (glycosaminoglycans). The crystalline structures can be identified using scanning electron microscopy

[21]. The heterotopic ossification seen in a 7 year old German Shepherd with fibrodysplasia ossificans may have resulted from the metaplastic change of calcinosis circumscripta lesions [22]. In this dog, several mineralized densities were seen radiographically ventrolateral to the lateral processes of the 6th cervical vertebra.

There have been several reports of calcinosis circumscripta/tumoral calcinosis (CC-TC) causing spinal cord compression in young dogs (usually less than 1 year of age) in several breeds including Bernese Mountain dog, German Shepherd, English Springer Spaniel, Rottweiler, and Great Dane [23-26]. With the exception of upper thoracic cord compression (T2 - T3) in two littermate German Shepherd puppies [25], all CC-TC masses resulting in spinal cord compression have been localized at the atlantoaxial articulation [23,24,26,27], often in the area of atlantoaxial ligament. The focal calcified masses are usually found lying over the spinal cord in the space between the caudal aspect of the dorsal arch of the atlas and the cranial edge of the spinous process of the axis, and extending into the vertebral canal. In the report involving the two young German Shepherd littermates [25], a solitary mineralized mass was found on the dorsal laminae between the dorsal spines of T2 and T3 and impinged ventrally on the intervertebral foramina. The mass projected above the articular facets between the dorsal spinous processes. Hematological and biochemical analysis of blood samples from affected animals are within normal limits, as is cerebrospinal fluid (CSF) evaluation. Clinical signs of CC-TC will reflect either a cervical syndrome or a thoracolumbar syndrome. Myelography will confirm spinal cord compression associated with these masses. Special imaging, such as computed tomography and computed tomographic myelography, may provide additional information on the extent of the mass and on the degree of spinal cord compression [26]. In the cases of CC-TC reported to date with spinal cord compression, the initiating mineralized mass lesion was the only lesion observed radiographically. There has been a report of unilateral and bilateral mineralized masses associated with the deep tendinous attachments on the lateral processes of the caudal cervical vertebrae [28]. In this report, the masses occurred in three related Great Dane puppies (around 5 to 6 months of age) but were non-clinical and only of cosmetic significance. Surgical removal of CC-TC masses in dogs with spinal cord compression is the treatment of choice and prognosis is favorable.

Reports of solitary cartilaginous exostoses in three young, large breed dogs (Rottweiler, Bernese Mountain dog, and St. Bernard), from 3.5 to 5 months of age [29], as well as in a 3.5 year old Bernese Mountain dog [30], may actually be further examples of CC-TC, or, at least variants. In each case, solitary, partially calcified lesions were localized to the atlantoaxial articulation and caused tetraparesis from spinal cord compression. The radiographic features appear identical to those described for CC-TC, including thickening of the dorsal arch of the atlas and malformation and shortening of the spinous process of the axis [23,26,29,30]. The histopathological features of the masses, however, appear to be different from those reported in CC-TC [5]. Surgical removal of the mass was successfully achieved in the older dog [30].

Note: I thank Dr. Roy Pool, Mississippi State University, for his valuable comments on this condition.

### **Cervical Spondylomyelopathy**

Cervical spondylomyelopathy is a neurological disorder affecting Doberman Pinschers, Great Danes and other large and medium-sized breeds in which abnormalities of the cervical spine cause compression of the spinal cord [31]. Synonyms include wobbler syndrome, cervical malformation-malarticulation, cervical vertebral instability, cervical vertebral malformation, vertebral subluxation, cervical spondylolisthesis, cervical stenosis, caudal cervical spondylomyelopathy, and cervical spondylopathy. Approximately 80% of cases occur in Great Dane and Doberman Pinscher dogs and lesions are generally confined to the caudal cervical spine (i.e., C5 to C7). The age of onset of clinical signs is variable, ranging from 3 months to 9 years. In general, Great Danes are affected less than 2 years of age, while Doberman Pinschers more frequently manifest signs when 2 years of age or older, with a clinical incidence peak between 4 and 8 years [32-34]. Several reports suggest male dogs are more commonly affected [35,36], although no gender predilection was revealed in one study involving 170 dogs [32]. Cervical spondylomyelopathy appears to involve both bony, fibrocartilaginous, and ligamentous abnormalities of the caudal cervical spine.

These include:

- a. Chronic degenerative disk disease,
- b. Congenital bony malformation (stenosis of the vertebral canal and abnormal articulation of the articular facets),
- c. Vertebral instability or "tipping",
- d. "Hourglass" compression by the dorsal (ligamentum flavum) and ventral (dorsal longitudinal ligament and dorsal annulus fibrosus) ligaments, and
- e. Hypertrophy of the ligamentum flavum. These changes, occurring alone or in combination, can result in caudal cervical spinal cord compression [32].

The cause of cervical spondylomyelopathy remains uncertain but it may be multifactorial. Some authors consider the disease

to be a developmental malformation-malarticulation disorder [35,37,274]. Hereditary factors have been suggested [38,39]. A possible familial trait was suggested for affected Dobermans in New Zealand [32]. Other reports failed to find support for a genetic basis, although recognizing the problem was more prevalent in certain lines of Dobermans [33,35]. Nutritional status has been implicated, including a hypercaloric diet and calcium excess in rapidly growing dogs [40-42], yet cervical spondylomyelopathy does occur in animals reared on a balanced diet [33]. The impact of conformation, such as longer neck and heavier head in affected dogs [42] playing a biomechanical role in this disease, was not confirmed in one study in which radiographic changes were independent of several body dimensions measured [32]. Interestingly, there was a positive correlation between longer rump length and increased risk of neurological disease in this study. Cervical trauma from use of a choker chain was not found to influence the presence of the disease [32].

Clinical signs are related to the severity of spinal cord compression and therefore are variable in nature and degree. Clinical signs usually are first noticed in pelvic limbs. Eventually, all four limbs are affected, with signs often being more pronounced in the pelvic limbs. There is ambulatory tetraparesis with the thoracic limbs moving in a short, choppy manner. The neck is often carried in flexion. There may be varying degrees of atrophy of infraspinatus and supraspinatus muscles. An affected animal can have difficulty rising from lateral recumbency or from a sitting position. The digits may knuckle when the animal walks and nails are often worn excessively as a result of scuffing and dragging. Most dogs have a conscious proprioceptive deficit and demonstrate a wide-based stance. Sometimes pain may be elicited upon neck manipulation. Clinical signs tend to be slowly progressive but can be abrupt in onset when external trauma is suspected as playing a major precipitating role. A Horner's syndrome may be present, perhaps more often in dogs with severely herniated intervertebral disks, especially at the C6 - C7 region [35].

Diagnosis is based on historical data, signalment, clinical data, and radiography. Most dogs have the following radiographic abnormalities [43]:

- a. Tipping of the craniodorsal aspect of the vertebral body into the spinal canal which may be exaggerated by neck flexion;
- b. Stenosis of the vertebral canal, especially at the cranial aspect of the vertebrae. Normal and abnormal values for vertebral canal dimensions have been established [32,44,275];
- c. Malformations of the vertebral bodies (see below);
- d. Narrowed disk spaces, often with accompanying spondylosis deformans; and
- e. Degenerative changes in the articular facets. These changes may be seen radiographically, alone or in combination.

In adult dogs, the most important abnormalities seen using survey radiography are narrowed intervertebral disk space, vertebral malalignment (e.g., tilting or subluxation), ventral spondylosis deformans, and a misshapen vertebral body [31,35,45]. Vertebral tilting and coning of the vertebral canal with stenosis of the cranial orifice is primarily recognized in dogs less than 1 year of age [31,32]. Vertebral changes may be seen radiographically in puppies as early as 3 months of age [32] and the observation of normal radiographic appearance of cervical vertebrae at 6 weeks of age in one of these puppies suggested the possibility of vertebral deformity occurring between the ages of 6 and 12 weeks.

Many animals have more than one site of compression, which may not be apparent on survey radiography. In one study, plain films were inaccurate in 18 of 45 dogs (40%) [46]. Therefore, myelography is essential to establish an accurate diagnosis and prognosis, especially if surgery is to be considered. Conventional myelography is considered the technique of choice for initial evaluation of dogs with cervical spondylomyelopathy since it provides an image of the entire cervical spine [47]. Furthermore, myelographic studies may reveal various types of extradural spinal cord compression:

- a. Dorsal compression associated with hypertrophied ligamentum flavum;
- b. Ventral compression from a bulging/hypertrophied annulus fibrosus;
- c. Lateral compression from malformation of articular facets;
- d. Compression from a stenotic vertebral canal or vertebral instability associated with vertebral tipping [43].

Some clinicians are advocates of stress radiography/myelography (i.e., use of flexion, extension, or traction of the cervical vertebrae) in order to better define the nature of the compressive lesion (dynamic versus static) and better define the subsequent treatment. The measurement of "stepping" of the vertebral floor of cervical vertebrae when the neck is flexed has diagnostic significance [33]. However, complications may follow stress radiography. Hyperflexion of the neck may exacerbate cord compression caused by vertebral tipping and neck hyperextension may aggravate cord compression by closing the dorsal aspect of the intervertebral disk space which can force additional disk material (nucleus pulposus and/or



annulus fibrosus) into the spinal canal. Neck hyperextension may also worsen pre-existing compression from the ligamentum flavum [43] (it remains to be proved whether or not the apparent increase in cervical hyperextension in the Doberman Pinscher breed as a whole, between 1934 and 1972, has a role in cervical spondylomyelopathy [47]). Conversely, with soft tissue lesions, traction on the cervical spine will often reduce the degree of cord compression by stretching or flattening redundant annulus fibrosus and ligamentous structures [31,46]. While non-contrast and intravenous contrast-enhanced computed tomography appears to have little advantage over conventional myelography in cervical spondylomyelopathy [47], other specialized imaging techniques may also play an important diagnostic role, e.g., computed tomography-myelography may provide more information than conventional myelography as to the exact nature and degree of compression, particularly in cases of severe spinal cord atrophy [47].

Gross pathologic findings include stenosis of the rostral end of the involved vertebrae, unstable vertebrae associated with flattened, expanded and elongated articular facets, and hyperplasia of the dorsal annulus fibrosus and ligamentum flavum in young animals. The abnormal relationship of one vertebra to another may result in static or dynamic cord compression. Similar changes occur in older animals along with degenerative lesions affecting the articular facets including osteophyte formation, sometimes with encroachment onto the spinal cord [48]. In older dogs, the fibers of the dorsal annulus fibrosus of the intervertebral disk appear hypertrophic or hyperplastic and may be partially or totally ruptured, with disk material extruded up beneath the dorsal annulus, although herniated disk material into the vertebral canal is infrequent. The nucleus pulposus may show degenerative changes and can be mineralized [35]. Disks at C5 - 6 and C6 - 7 are most frequently affected [33,35,49]. In both young and older dogs, gross vertebral deformity may be found, often involving C6 and/or C7 in Dobermans and Great Danes [33,35,50]. The deformity can vary from rounding off of the cranioventral epiphysis to its total loss producing a triangular wedge-shape. Redundant ligamentum flavum resulting in dorsal cord compression is reported in Great Danes [46]. Similarly, the above-mentioned hourglass compression by dorsal and ventral ligaments as well as joint capsule of the facets, is seen principally in Great Danes [31]. In the spinal cord, varying degrees of compression and spinal cord atrophy may be present. Degenerative changes characterized by white and gray matter necrosis, neuronal loss, and cavitation may be seen at the site of spinal cord compression. At this level, lesions may be seen in all funiculi. Wallerian-like degeneration of white matter is seen above (e.g., ascending tracts in the dorsal funiculi and more superficial portions of dorsolateral funiculi) and below (e.g., descending tracts in ventral and deeper portions of lateral funiculi) the compressive lesion [37]. Myelin degeneration is often more predominant than axonal degeneration. Arachnoid fibrosis is not uncommon.

Prognosis for spontaneous recovery is poor. In mildly affected cases, conservative treatment may sometimes be beneficial over a 4 to 6 week period. This includes strict confinement, neck brace to immobilize the caudal cervical spine, and anti-inflammatory medication. However, long-term conservative therapy tends to be palliative [49]. Marked improvement has been reported in many cases following decompressive and/or stabilizing surgery.

A plethora of reports are available on surgical treatment that generally falls into three categories:

- a. Dorsal laminectomy for bony compression,
- b. Ventral slot decompression, which is especially useful for ventral soft tissue compressions that are not traction-responsive (such as annular protrusions or nuclear extrusions), and
- c. Distraction or ventral slot decompression for traction-responsive soft tissue compressions [34,51-58]. Distraction may be achieved with vertebral body pins/screws and bone cement, distraction rods, or intervertebral washers, often in association with bone grafts in order to encourage vertebral fusion [31,52,59].

The choice of surgical technique will vary according to the location of spinal cord compression (ventral, dorsal, or lateral), the nature of the compression (soft tissue or bony), and whether or not the lesion is single or multiple: up to 30% of cases in mature Dobermans may have multiple protrusions of the annulus fibrosus [34,53]. The most common lesions are ventrally located, involve soft tissue, and tend to be traction-responsive [31,46]. All surgical procedures have a high potential for morbidity and post-operative complications, which include infection, implant failure, and additional disk protrusions ("domino effect") in disks adjacent to fused or immobilized segments [49,53,60]. It has been reported that short-term success rates are high (approximately 80 per cent) after any of the surgical procedures, but there is a high rate of recurrence (around 20 per cent) [276]. Iatrogenic Horner's syndrome has been reported associated with cervical surgery, presumably due to traumatic stretching of preganglionic pathways in the thoracic vagosympathetic trunk within the carotid sheath [61]. Furthermore, neurological signs may be more pronounced the day following myelography in dogs with cervical spondylomyelopathy [62]. Non-ambulatory patients require special care and intensive nursing (see spinal trauma) for bladder control and prevention of urine scald and decubital ulcers. Physical therapy (see rehabilitation) is extremely important to combat disuse and neurogenic muscle atrophy [49,63]. One suggested prognostic guide is as follows [64]:

1. Favorable - If there is one lesion and the dog is ambulatory upon presentation;
2. Favorable to guarded - If there are two lesions and the dog is ambulatory upon presentation;
3. Guarded - If there is one lesion and the dog is non-ambulatory upon presentation;
4. Guarded to unfavorable - If there are two lesions and the dog is non-ambulatory upon presentation.

The demonstration of spinal cord atrophy and/or pooling of contrast material within the spinal cord in computed tomography-myelographic studies may also suggest a guarded to unfavorable prognosis in dogs with cervical spondylomyelopathy [47].

Control measures might include identifying Dobermans with radiographic features of cranial canal stenosis, vertebral tipping, and "stepping" of the cervical vertebrae once skeletal maturity has been reached and removing them from any breeding program since these identifiable abnormalities offer a reasonably accurate prognostication for future development of cervical spondylomyelopathy in this breed [33]. Additionally, use of balanced rations without excessive nutrition or mineral supplementation and perhaps neutering larger, faster-growing puppies might be considered [33]. Cervical vertebral ratios may have potential as a breed-specific screening tool for cervical vertebral instability [275].

There have been isolated reports of a similar wobbler syndrome in other canine breeds including Rhodesian Ridgeback, Old English Sheepdog, Weimaraner, German Shepherd, Chow Chow, Rottweiler, Pyrenean Mountain Dog, Golden Retriever, Labrador Retriever, Boxer, Irish Wolfhound, St. Bernard, Airedale Terrier, Bernese Mountain Dog, Bull Mastiff, English Setter, Irish Deerhound, and Old English Mastiff. In these breeds, the predominant sites of cord compression were C2 - C3 and/or C3 - C4 [35]. A possible hereditary malformation of C2 - C3 vertebrae occurs in Basset Hounds less than 8 months of age [65]. Involvement of the C2 - C3 articulation has been noted in Beagles [35].

The wobbler condition has also been reported in older female Borzoi dogs (from 5 to 8 years) [66]. The condition is believed to have a recessive mode of inheritance. The C6 - C7 articulation was always involved in a spectrum of abnormalities that included vertebral instability, vertebral luxation, intervertebral disk herniation, and spinal cord compression.

### Disk Disease

Spinal cord compression secondary to intervertebral disk protrusion-extrusion continues to be one of the most common neurological disorders seen in clinical practice [67]. Terms used for this disorder include ruptured disk, prolapsed disk, slipped disk and herniated disk. Disk protrusion-extrusion more accurately describes this process. *Protrusion* implies that the disk is bulging into the vertebral canal as a result of dorsal shifting of central nuclear material. The outer fibrous envelope of the disk is still intact. Disk *extrusion* indicates that the outer fibrous layers have ruptured with subsequent extrusion of nuclear material into the vertebral canal. The clinical expression of disk extrusion is referred to as *disk disease*. The term *intervertebral disk displacement* is presently in vogue as another descriptor of disk disease.

There are 26 intervertebral disks in the canine and feline spinal column, excluding the coccygeal region, and they form approximately 18% of the length of the spine. Disks are widest in the cervical and lumbar regions, and narrowest in the thoracic spine. Each disk consists of two structurally different regions: (a) a central gelatinous area, the nucleus pulposus (NP), and (b) a surrounding fibrous envelope, the annulus fibrosus (AF), which contains an inner, more fibrocartilaginous matrix termed the "transitional zone" (TZ) [68-71]. The NP is oval-shaped and eccentrically positioned between the middle and dorsal thirds of the disk. It is a highly specialized tissue originating from the embryonic notochord. Throughout fetal life, the NP is the fastest growing region of the disk, and in the neonate, it occupies a considerable area of the disk. The AF is a fibrocartilaginous tissue consisting of bands of parallel fibrous bundles that run obliquely between adjacent vertebrae. The ventral annulus is about twice as wide as the dorsal annulus. Biochemically, the major macromolecular components of the canine disk include collagenous and non-collagenous protein (NCP), proteoglycan (PG) aggregates, and glycoproteins. The PG subunits consist of glycosaminoglycans (GAGs) covalently bound to a central protein core. The main GAGs in canine intervertebral disks are hyaluronic acid, chondroitin sulfate-4, chondroitin sulfate-6, and keratan sulfate. Higher orders of aggregation intimately involve hyaluronic acid. Aggregated PGs are formed by the association of many PG molecules with a single chain of hyaluronic acid, the complex being stabilized by a glycoprotein link. The GAGs are long-chained, sulfated polyanions that attach to the central protein core like the bristles of a brush. The greatest concentration of the GAGs in disk occur in NP and TZ regions of the disk.

Structures that are anatomically and physiologically closely related to disks include cartilaginous end-plates, vertebral end-plates, and conjugal and dorsal longitudinal ligaments. Conjugal ligaments, also known as transverse intercapital ligaments, are present between the second and tenth thoracic vertebral bodies in dogs, and between the second and ninth thoracic vertebral bodies in cats. Conjugal ligaments run over the dorsal part of the disk, ventral to the dorsal longitudinal ligament (a flat structure that lines the floor of the vertebral canal), and connect the heads of each set of ribs. The conjugal ligaments play an important role in the prevention of disk extrusion into the vertebral canal in the thoracic region. Dorsal longitudinal ligaments run the length of the vertebral canal, are attached to the dorsal borders of the vertebral bodies and form fan-like

coverings over the dorsal aspects of each disk. Stretch of this ligament is thought to partially account for pain associated with disk protrusion-extrusion. Cartilaginous end-plates are thin layers of hyaline cartilage that cover vertebral body epiphyses and form the rostral and caudal boundaries of each disk. Vertebrae on either side of the disk have a specialized plate of dense, smooth bone termed the vertebral end-plate. These plates are perforated by numerous small canals that are related to the underlying marrow spaces. Each plate consists of an outer peripheral zone and an inner zone that accommodates the NP region of the disk.

Intervertebral disks function as very effective shock absorbers of the vertebral column, largely due to the gel-like properties of the central NP. Specialized PGs within the nucleus bind many water molecules to form a fluid system that is virtually incompressible. This hydrophilic property allows the nucleus to deform and dissipate forces equally over the AF and cartilaginous end-plates. The transformation of an axial compressive force applied to the spine into tangential stresses on the annulus is the function of the NP, thereby reducing the compressive force on the annulus itself. Disks also provide support for the spinal column, since they represent amphiarthrodial joints in intervertebral articulations.

After birth, the canine disk undergoes structural changes that are most prominent in the NP [71-73]. The gel-like nucleus is eventually replaced by more mature fibrocartilage. This process occurs gradually in most breeds of dogs, so that by 7 to 8 years of age, the entire nucleus has changed, and the distinction between nucleus and annulus is lost. In several other breeds of dogs, however, the aging pattern is quite different. These breeds have been designated *chondrodystrophoid* due to their characteristic endochondral ossification and intervertebral disk morphology, and include Dachshunds, Beagles, Pekingese, French Bulldogs, Basset Hounds, Welsh Corgis and Cocker Spaniels [70,71]. Such breeds are characterized by varying degrees of short-limbed dwarfism. Other breeds such as Shih-tzus and Lhasa apsos probably should also be included in this group. In chondrodystrophoid breeds, replacement of notochordal cells and the gelatinous NP occurs as early as 4 months of age. This process is generally complete in all disks by 12 to 18 months of age. The central areas of the NP are usually the last to be affected, and extensive degenerative changes frequently precede the final chondrification of this area. With increasing age, degenerative changes observed in the NP include matrix disintegration, peripheral/central calcification, and localized areas of cell death. Radial fissures and clefts may appear in the AF. Commensurate with the morphologic transmutation of the NP, collagen levels approach 30 - 40% dry weight within 6 - 12 months. Extraordinary changes in all other biochemical parameters occur during the first 2 to 3 years [74-76]. In comparison with disks from non-chondrodystrophoid animals of similar age, PG levels in NP are 40 - 50% lower, glycoprotein and non-collagenous protein values are 30 - 40% lower, and chondroitin sulfate values are 30 - 50% lower. Also, during this period, keratan sulfate replaces chondroitin sulfate(s) as the major GAG. The degree of hydration of disks likely decreases with reduction in GAG content, as has been shown in people. Degenerated disks have a depressed imbibition index, which is a measure of the water-binding capacity of the disk.

The etiology of intervertebral disk protrusion-extrusion remains elusive. It is hypothesized that significant changes in morphology and biochemical parameters of the disk during the first 2 years of life result in a reduction of the disk's shock absorbing mechanisms [68,69]. While still retaining limited properties of incompressibility, the NP loses its ability to adequately deform and distribute forces in a centrifugal manner. As a result, the AF is subjected to increased loading from axial compression and lower tangential stress, which is disproportionately distributed in the disordered disk. The mechanical failure of the NP ultimately results in disruption of AF fibers and subsequent protrusion-extrusion. Results of biochemical studies suggest that the mechanical efficiency of disks is compromised in chondrodystrophoid dogs by 2 to 3 years of age [74-76]. This time-frame is consistent with the occurrence of clinical disease. Nevertheless, this theory does not explain why clinical disk disease occurs with a relatively high frequency in some non-chondrodystrophoid breeds, such as Miniature Poodles and mixed-breeds; nor does it elucidate why clinical disk disease occurs infrequently in older dogs of any breed. Studies in dogs have shown that disk metabolism in the NP is mainly anaerobic, the main route of nutrient supply into the NP is via the endplate, and that diffusion of nutrients is the main mechanism of metabolite transport [77]. There is probably an optimal, but as yet undefined, range of vertebral stress that is needed to promote and maintain nutritive requirements of disks. Half an hour of moderate exercise per day has been shown to increase nutrient flow into canine disks [78]. In contrast, spinal fusion in the dog results in significant biochemical changes in disks-metabolism is depressed in the immobilized disks but increased in the disks adjacent to the fusion mass [79]. In addition, water content and imbibition of water in NP and AF are significantly depressed in fused disks. That disk displacement occurs with some frequency in disks adjacent to totally calcified disks may also reflect an overstressed disk. Finally, it is conceivable that loss of PGs and mechanical failure of the NP profoundly influence disk nutrition. Whether disk matrix changes are the cause or the effect of nutritional diffusion impairment remains to be determined.

There is no evidence that external trauma plays a role in disk degeneration. A force of sufficient magnitude to result in spinal fractures and/or luxations rarely produces traumatic disk protrusion-extrusion. Nevertheless, trauma has been implicated in several large-breed, non-chondrodystrophoid dogs in which tearing of the dural mater secondary to intervertebral disk injury occurred during periods of vigorous running and or struggling [80]. Although trauma does not appear to play a role in the initiation of disk degeneration per se, it may be a factor in the precipitation of protrusion-extrusion once the normal mechanical efficiency of the disk is impaired. It is not unusual for dogs with clinical disk disease to be presented with a

history of spinal trauma of variable degree, such as jumping or falling. Perhaps the most logical explanation for the prevalence of disk disease in certain breeds of dogs is a genetic one. Earlier studies suggested that genetic factors are involved in the accelerated aging patterns of disks in Beagles [81]. The heightened susceptibility to disk disease in Dachshunds has been explained by a genetic model that involves the cumulative effect of several genes, with no dominance or sex linkage, subject to environmental modification [82]. In some families of Dachshunds, the prevalence of disk disease was found to be 62%, compared with the estimated breed prevalence of 19%. Genetic osteological factors probably play a role as well. For example, midsagittal and interpedicular diameters of the cranial and caudal aspects of cervical vertebral foramina (C3 - C7) are reportedly significantly larger in small breeds than in large breeds and Dachshunds, with seemingly potential predisposition to cervical spinal cord compression [274]. There is no evidence that autoimmune mechanisms are a factor in the pathogenesis of disk degeneration. The roles of inactivity and obesity in disk disease have not been fully evaluated, although in one study, excess body weight did not appear to be a predisposing factor in Cocker Spaniels with disk disease [83].

Neurological signs after extrusion of disk material are caused by impact injury [84], or mechanical compression of the spinal cord [85], or both. While disk protrusion usually precedes extrusion, protrusion or bulging of the disk dorsally into the vertebral canal without rupture of the AF is not usually associated with clinical signs, with the possible exception of pain. This is exemplified in dogs and cats over 7 years of age in which dorsal disk protrusion is relatively common but is subclinical. The velocity with which the disk material extrudes into the canal appears to be more important than the size of the mass. An explosive herniation results in far more severe damage than a slow extrusion. With acute impact injuries, hemorrhage and attendant inflammatory reaction may also contribute to epidural compression. Results of a quantitative radiographic study [86] suggest that the lumbar epidural space in Dachshunds is less than that in German Shepherds (a non-chondrodystrophoid breed) which implies that epidural masses of similar size would cause more spinal cord compression and more severe neurological deficits in Dachshunds. For a review of the pathophysiological events and biochemical cascade occurring with acute trauma to the spinal cord see spinal cord trauma.

Most dogs with disk disease are between 3 and 7 years of age. Eighty-five percent of disk extrusions in dogs occur in the thoracolumbar area and 15% are cervical. Approximately 80% of thoracolumbar extrusions occur between T11 and L3, with less than 2% occurring in the terminal lumbar region (L5 - S1). In one study of large-breed, non-chondrodystrophoid dogs with thoracolumbar disk disease, the mean age was approximately 7 years, and 57 dogs (92%) had Hansen type 1 disk disease, usually at the L1 - L2 site [87]. In this report, 58% of cases were acute in onset. Disk extrusion normally does not occur between T2 and T10, probably because of the presence of the conjugal ligament, although a Hansen type 1 disk extrusion has been reported at the T1 - T2 level in a 7 year old Dachshund with acute neurological deficits to the hind limbs following trauma [88]. Several studies indicate that the most common site in the cervical region is C2 - 3 [89,90]; although results of one study (105 cases) indicated no significant difference in prevalence of disk disease affecting the first four disk spaces (C2 - 3 to C5 - 6) [91] (in this study, prevalence of disk disease at C7 - T1 was significantly less than that involving the first 4 disk spaces).

Disk disease also occurs in cats but mainly as a subclinical event [89]. One study on clinically normal cats showed that degenerative changes in disks increased with age, with dorsal protrusions found in 30% of cats 6 to 10 years of age, in 50% of cats 11 to 14 years of age, and in all cats 15 years of age and older [92]. In another report, type I disk protrusion in cats, again as a subclinical condition, was encountered most commonly in upper cervical and L4 - L5 areas [93]. Nevertheless, clinical signs of disk disease have been reported sporadically in cats [94-96]. In a recent study of disk disease in 10 cats, there was no breed or sex predilection and clinical signs included back pain, difficulty ambulating, and incontinence [96]. All herniations occurred in the thoracolumbar spine, with a peak incidence at the L4 - L5 disk space. Eight cats had a Hansen type I protrusion.

The onset of clinical signs in dogs may be acute (minutes), subacute (hours), or chronic (several days or weeks). These signs may be rapidly progressive, slowly progressive, or may remain static. Clinical signs also may undergo remission, only to recur at a later date. Clinical signs in dogs with recurrent attacks frequently are more severe than those seen at the initial episode. Recurrences have often been considered to be the result of multiple extrusions at the same disk level [97,98]. However, in a recent study, 22 of 25 dogs had a second operation (> 4 weeks after the initial surgery) at a site distinct from the initial lesion [99]. In this study, Dachshunds were at higher risk for recurrences than other breeds.

The two most common neurological syndromes associated with disk disease are thoracolumbar and cervical syndromes. With cervical disk disease, the majority of affected animals will have a history of pain, with or without paresis [90], and frequently, spasms of cervical musculature. Animals may assume a posture with the nose held close to the ground and the back arched. In some dogs, one thoracic limb may be held in partial flexion, with reluctance to support weight or walk on this limb. These animals frequently show considerable pain on manipulation of the head and neck. This combination of signs is termed *root signature*, since it is believed to be associated with nerve root entrapment near the intervertebral foramen as a result of lateral

disk extrusion [100]. A **lumbosacral syndrome** is uncommonly associated with disk disease. In some animals with lumbosacral disk extrusion, one pelvic limb may be held in partial flexion or a repetitive "stamping" motion may be observed. These animals frequently show considerable pain on manipulation of the limb and lumbosacral spine. This combination of signs has also been termed *root signature* and is believed to be associated with nerve root compression or entrapment by a fragment of extruded disk material. In a small percentage of dogs, a multifocal syndrome may develop as a result of an acute, explosive extrusion of disk material from a thoracolumbar disk that produces hemorrhagic myelomalacia. With this irreversible disorder, an initial thoracolumbar syndrome may be followed by a lumbosacral syndrome as the lesion descends the cord. As the lesion also frequently ascends the cord, signs of thoracic limb rigidity give way to flaccidity and areflexia followed by death due to respiratory paralysis.

A definitive diagnosis of disk disease requires radiographic confirmation of presence of a mass lesion or, in absence of a mass lesion, evidence of characteristic changes in the disk-vertebral articulations. Typical radiographic features of disk disease include narrowing of the disk space, intervertebral foramen and articular facet at the site of the herniated disk, wedging of contiguous vertebral bodies so that the dorsal part of the disk space appears narrower than the ventral part, and presence of an opacified mass in the vertebral canal. *In situ* calcified disks, in the absence of any other abnormality, are a common finding in chondrodystrophoid breeds of dogs and are of little significance-it has been estimated that dystrophic calcification occurs in 20 to 77% of disks in some chondrodystrophoid breeds within the first year or two of life [71,101-103], especially in Dachshunds in whom calcification appears to be inherited [104,272]. Recent studies suggest that exercise has a modulating effect on rate of occurrence of disk calcification in Dachshunds (moderate exercise reduced the rate of occurrence of disk calcification) [105]. In some cases, particularly in acute extrusions, plain radiographic findings may be minimal or equivocal and myelographic studies will be necessary to define the extent and location of spinal cord compression. In one study, accuracy for determining sites of intervertebral disk protrusion using survey radiography was only in the 51 - 61% range [280]. The importance of accurate localization of lesions is demonstrated by the presence of asymmetrical neurological signs contralateral to the myelographic and surgical lesion in some dogs, especially those with Hansen type 1 extrusion [106]. Contrast studies also are indicated when there is evidence of more than one disk lesion. The most common myelographic change is narrowing and dorsal deviation of the ventral contrast column at the level of disk protrusion/extrusion. If the disk extrusion is acute, spinal cord swelling may result in complete blockage of contrast material at, or immediately rostral to the level of the disk extrusion. Note that dogs with thoracolumbar or cervical disk disease that have clinical signs of back or neck pain alone, without neurologic deficits, may have substantial compression of the spinal cord [90,107]. Results of experimental studies suggest that high-dose contrast enhancement (e.g., 0.3 mmol/kg of gadoteridol) might facilitate the detection of recurrent herniated disk fragments [108]. While plain radiography and myelography have long been the methods of choice for the diagnosis of disk disease, other non-invasive neuroimaging procedures such as magnetic resonance imaging (MRI) [109] and computed tomography (CT) [110-112] may be more accurate, technically easier, and safer (myelography may exacerbate clinical signs and induce seizures). In one report, preoperative CT confirmation of the relationship between the spinal cord and the protruded disk was used in planning the surgical approach in dogs with cervical disk disease [113]. MRI is considered to give better information about the condition of the intervertebral disk (e.g., the hydration status of the nucleus pulposus) than radiography [114]. In fact, classification of degenerating intervertebral disks and identification of MR imaging characteristics of each type have been reported in experimental studies in dogs [115]. Hemorrhage may also be identified using MRI [278]. Analysis of CSF, especially if sampled from the lumbar subarachnoid space, may reveal markedly elevated protein levels and increased numbers of mononuclear white blood cells [116]. These changes are more likely to be found in dogs with severe and acute neurological signs. Recent studies have shown a significant increase in lumbar CSF glutamate concentrations in both acute and chronic cord compression injuries secondary to disk herniation in dogs [117].

Gross pathological findings occurring subsequent to disk disease usually depend on whether disk protrusion-extrusion is partial or complete and whether it occurs acutely or gradually. While many disks in older animals of any breed may protrude, it is uncommon to find more than one extruded disk, even in animals that have had a history of multiple episodes. This suggests that many recurrences are due to multiple extrusions from single disks (see below). In disk protrusion, the AF may bulge dorsally into the vertebral canal, without rupturing. This is known as a Hansen type 2 disk [71], and it appears as a small, round to dome-shaped bulging of the dorsal surface of the disk. A **Hansen type 1 disk** [71] is characterized by rupture of the dorsal annulus, with extrusion of degenerate NP into the vertebral canal around the spinal cord. In some instances, the extruded nuclear material will be contained by the dorsal longitudinal ligament. Typically, disks extrude in a dorsomedian, paramedian, or dorsolateral plane. In the cervical region, where the vertebral canal/spinal cord ratio is larger than that of the thoracolumbar region, lateral and intraforaminal extrusions may be more common than in other spinal regions, producing spinal root rather than spinal cord compression. Rarely, disk material may herniate through the cartilaginous end-plate into the vertebral body (resulting in an intravertebral herniation or Schmorl's node) [118], or into the spinal cord itself

(intramedullary extrusion) [279].

The spinal cord may be swollen, indented, flattened, or atrophic. In chronic cases, a fibrous adhesion may be evident between the extruded mass and the dura mater. In many instances of Hansen type 1 disk extrusion, hemorrhage will be associated with the extruded disk material, producing a soft, granular, salt and pepper consistency. In some cases, the volume of epidural hemorrhage may exceed that of the extruded disk material. The extruded material may form a circumscribed mass or may lie flattened around the sides of the dura mater. The extruded material may have migrated one or two vertebral levels away from the site of the affected disk. This form of extrusion is usually present in dogs with thoracolumbar disk disease. Since extruded disks are not completely absorbed, single disks that may have had multiple extrusions are recognized by their stratified appearance. The oldest component may be dark gray, hard, and adherent to the dura. Subsequent laminations are lighter in color and more friable [97]. In chronic disk disease with slow, progressive extrusion, the degenerate material frequently has a gritty consistency and an opaque and cheesy appearance. This type of extrusion is more often observed in dogs with cervical disk disease.

Microscopic changes in the spinal cord are dependent on the rate of disk extrusion and duration of cord compression. Gradual or mild compression produces varying degrees of demyelination and axonal degeneration. Sudden, massive extrusions often result in focal or multifocal hemorrhage and necrosis in gray and white matter. Localized edema may result in pronounced cord swelling and collapse of the subarachnoid space. Rarely, disk material will be present within the cord parenchyma. In necrotic areas of the spinal cord, vessels and mesenchymal (connective tissue) elements are usually preserved. Lipid macrophages are observed in those cases of a few days duration. In more chronic cases, marked proliferation of astrocytes and microglial cells may be a feature, especially in areas that border the necrotic zone, together with trabeculae of blood vessels and connective tissue that cross the necrotic areas [84]. In longer standing lesions, the gray matter often has a fenestrated appearance due to loss of neurons and fibers. Astrocytic gliosis may result in marked sclerosis of the gray matter. An epidural inflammatory reaction composed of neutrophils, red blood cells, fibroblasts, large mononuclear cells, occasional multinucleate giant cells, chondrocytic-like cells, and fibrocartilaginous debris may be present.

Medical management usually is directed at animals with their first signs of disk disease. Mild clinical signs often resolve after at least three weeks of confinement with outside activity limited to leash exercise. Recurrences of clinical signs are common in this group of animals. Severe, unremitting pain may be managed with prednisolone, 0.5 mg/kg, PO, bid, for 72 hours. Muscle spasms may respond to muscle relaxants, e.g., methocarbamol (Robaxin), 20 mg/kg, PO, tid, for 7 to 10 days, or diazepam, 2 - 5 mg, PO, tid, for several days. High dose methylprednisolone succinate should be considered in paraplegic/tetraplegic animals with acute spinal cord injury (see spinal trauma). Acupuncture is considered another form of conservative treatment [119-122]. The analgesic response to acupuncture is reportedly most effective in dogs showing pain with or without mild paresis. Animals receiving this treatment should have restricted activity.

Surgical treatment is indicated in animal with clinical signs unresponsive to medical management, recurrent and/or progressive clinical signs, or in animals that are paralyzed. The approaches most widely used are dorsolateral hemilaminectomy / pediculectomy or dorsal laminectomy for thoracolumbar disk disease and ventral slot-decompression for cervical disk extrusions, although a thoracolumbar lateral approach has its proponents [89,123-128]. In a recent study, significant improvement in clinical results was seen in caudal cervical disk protrusions when additional surgical distraction and stabilization were provided following ventral slot decompression [129]. Dorsal laminectomy has also been successfully performed in dogs (especially those < 15 kg) with cervical disk disease [130]. While some studies of thoracolumbar disk disease indicate that removal of disk material using these techniques significantly improves the degree of completeness of recovery [131], successful results have been reported using fenestration alone [98,132-134]. Prophylactic fenestration [89] in addition to decompression remains somewhat controversial [135] but is still performed by many surgeons in order to reduce the chance of subsequent herniation involving other disks [136-138]. A variety of other surgical procedures have been described, including percutaneous discectomy [139], but their effectiveness await large clinical trials. Although still not commonly employed for the treatment of disk disease, chemonucleolysis (e.g., using collagenase or chymopapain injected directly into the disk) has its exponents [140-143] and may be more effective than fenestration at removing nuclear material from the disk [144]. Experimental autographic disk transplantation for potential use in humans with chronic disk disease is in its infancy but initial surgical studies in dogs showed promise [145]. Potential treatment complications include cardiac dysfunction from manipulation of the vagosympathetic trunk during cervical surgery, and vertebral luxation as a complication of the ventral slot procedure, especially in mid to lower cervical vertebrae [146]. Furthermore, cervical vertebral fusion may predispose adjacent disks to herniation [147]. Corticosteroid therapy (usually associated with use of dexamethasone) may lead to gastrointestinal hemorrhage, ulceration, colonic perforation and pancreatitis [148-150]. Complications may be kept to a minimum by administering corticosteroids for as short a time as possible. Prophylactic use of intestinal protectants, e.g., bismuth subsalicylate (Pepto-Bismol®) in conjunction with frequent administration (at least four times daily) of antacids, e.g., magnesium or aluminum hydroxide, or H2 antagonists such as cimetidine (Tagamet®, at 20

mg/kg, PO, tid) also may reduce the prevalence of gastrointestinal hemorrhage. Corticosteroids should be stopped immediately, when gastrointestinal complications are noted. In a recent study in dogs with acute degenerative disk disease treated by surgery and corticosteroid administration, both omeprazole (a gastric acid pump inhibitor) and misoprostol (a synthetic prostaglandin E1 analog) were ineffective in treating or preventing the further development of gastric mucosal lesions [150].

Paralyzed patients need to be maintained in a sanitary environment, with twice daily bladder catheterization, frequent removal of soiled bedding, and use of foam rubber pads or water beds to prevent development of decubital ulcers. In addition, active physiotherapy (see also spinal trauma and chapter on rehabilitation) that includes assisted standing and walking exercises, and supervised swimming for 15 minutes twice daily, is an integral part of the nursing care since it will delay disuse muscle atrophy.

The following statements may be used as a general guide to assess prognosis:

1. Animals that are paretic or paralyzed but have normal pain sensation have a good prognosis following medical and/or surgical management. Results of a recent surgical study (using hemilaminectomy and fenestration) with an 86% success rate indicated that the rate of onset of clinical signs significantly influenced the clinical outcome but not the length of recovery time, while the duration of clinical signs did not seem to significantly affect the outcome, but did affect the length of recovery time [281]. The presence of postoperative voluntary motor function is also reported to be a favorable prognostic indicator for early return to ambulation [282].
2. Animals that are paralyzed with loss of bladder control and with reduced pain sensation have a guarded-to-favorable prognosis following surgical intervention (decompression and/or fenestration).
3. Animals that are paralyzed with loss of bladder control and loss of pain sensation have a guarded-to-unfavorable prognosis.

Dogs with absent deep pain perception that undergo surgery within 12 to 36 hours have a better chance of recovery (more complete and over a shorter time-period) than those in which surgery is delayed [100]. Evaluation of the degree of myelographic spinal cord swelling might also assist in establishing a prognosis in severely affected animals [151]. As a caveat to prognostication, several studies have shown that severity of spinal cord dysfunction, based on clinical signs, does not necessarily predict outcome. In one recent report, 50% of dogs with loss of bladder control and loss of deep pain sensation recovered completely or partially [152].

A functional scoring system for pelvic limb gait of dogs with acute thoracolumbar spinal cord trauma (from spontaneously-occurring disk disease) has been developed to allow quantification of recovery to be assessed and potentially facilitate evaluation of pharmacotherapeutic clinical trials [153]. Spinal cord evoked potentials and somatosensory potentials may be useful in localizing spinal cord lesions and assessing lesion severity [154,155]. Other evoked potentials such as magnetically elicited transcranial motor evoked potentials may be sensitive indices of severity of spinal cord lesions in dogs with disk disease but do not appear to be reliable predictors of neurologic recovery [156]. In one report involving 10 cats with disk disease, prognosis was adjudged to be most favorable in cats following surgical decompression [96].

### **Diskospondylitis**

Diskospondylitis is intervertebral disk infection with concurrent osteomyelitis occurring in contiguous vertebral bodies [157-169]. This disorder occurs in young to middle-aged adult dogs (typically non-chondrodystrophoid) usually of the larger breeds. Male dogs outnumber females by approximately 2:1. Diskospondylitis has also been reported in cats, albeit infrequently [170-174]. Diskospondylitis may occur following iatrogenic trauma of the vertebral column (e.g., disk curettage), foreign body migration, paravertebral injection, extension from a body organ abscess, or more commonly from blood-borne septic emboli that reach the avascular intervertebral disk via the capillary networks in the vertebral end-plates [158-161,175,176]. The source of infection is not established in most cases. Possible initiating sites include the genitourinary tract, skin, gingiva, and infected heart valves. In one dog, epidural abscess and diskospondylitis developed after administration of a lumbosacral epidural analgesic [177]. Diskospondylitis has also been found in a Bernese Mountain dog with immune-mediated polyarthritis [178]. Bacterial infection is the most common cause of diskospondylitis and coagulase positive *Staphylococci* (*S. aureus* or *S. intermedius*) are the most frequent isolates. Other organisms identified include *Brucella canis*, *Nocardia*, *Streptococcus canis*, *Escherichia coli*, *Acaligenes* sp, *Micrococcus* spp, *Proteus* sp, *Corynebacterium diphtheroides*, *Mycobacterium avium*, *Erysipelothrix tonsillarum* and *Actinomyces viscosus*. In a recent study, novel organisms incriminated in canine diskospondylitis included *Pseudomonas aeruginosa*, *Enterococcus faecalis* and *Staphylococcus epidermidis* [179]. Fungal organisms including *Aspergillus terreus*, *Paecilomyces* sp (e.g., *Paecilomyces varioti*), *Penicillium* sp, *Chrysosporium* sp, *Pseudallescheria boydii*, and *Coccidioides immitis* have also been cultured [163,164,166,180,181]. In one retrospective study involving 135 dogs with diskospondylitis, the prevalence of dogs with

*Brucella canis* was approximately 10% and sexually intact male dogs were at risk as were dogs from the southeastern United States [182]. Immunosuppression may predispose some breeds, such as German Shepherds, Airedale Terriers, and Basset Hounds to bacterial or fungal infection and subsequent diskospondylitis [181,183-185]. Respiratory or gastrointestinal portals of entry are suggested for animals with aspergillosis. Curiously, the majority of reports of disseminated aspergillosis in dogs have involved German Shepherds [181,186-188] with organisms localizing most frequently in kidneys, spleen, and vertebrae. In one dog with diskospondylitis due to *Aspergillus terreus*, multiple granulomas with fungal elements were also found in the subarachnoid space associated with the nerve roots of the cauda equina [183]. Hypothyroidism does not appear to be a predisposing factor in the development of diskospondylitis.

Clinical signs are variable according to vertebral involvement, ranging from subtle spinal hyperesthesia and stiffness, to severe paresis/paralysis. In more than 80% of affected dogs, spinal pain is observed [189]. Affected animals may manifest depression, anorexia, and pyrexia. Often they are reluctant to exercise or jump. Heart murmurs can be detected on auscultation in some animals. Pleural effusion associated with paecilomycosis was reported in one dog [284]. Spinal cord and/or nerve root compression may result from proliferation of inflammatory tissue and exostosis, subarachnoid or epidural abscessation, vertebral pathological fractures, intervertebral disk protrusion/herniation, or excessive vertebral instability [177,187,190,191]. Spinal cord myelitis may also occur by extension of infection through the meninges.

Radiographic abnormalities include a concentric area of lysis of adjacent vertebral end-plates early in the disease process. More chronic lesions are characterized by varying degrees of bone lysis and proliferation, vertebral sclerosis, shortening of vertebral bodies, narrowed intervertebral disk spaces, and ventral osseous proliferation that may bridge the affected disk space. Extensive destruction of a vertebra may result in its collapse. Diskospondylitis may be present in more than one disk space and commonly occurs in one or more adjacent disk spaces. Common sites of diskospondylitis are the caudal cervical area, midthoracic and thoracolumbar regions, and the lumbosacral joint. In dogs with grass awn migration, reactive bony changes may be seen on ventral and lateral surfaces of vertebrae L2 through L4 [189]. The nature and location of the changes along the spine may help differentiate diskospondylitis from malignant bone disease [192]. The severity of the radiographic changes do not necessarily correlate with the degree of clinical involvement. Results of a recent multicenter, retrospective study evaluating contrast radiographic findings (myelograms or epidurograms) in canine bacterial diskospondylitis revealed that 15 of 27 cases (56%) showed some degree of spinal cord compression, although in the majority (approximately 73%) soft tissue was the compressive mass and the median compression for all cases was only 5% of the vertebral canal [193]. Vertebral subluxation was evident in 20% of these dogs. Stress radiography has been recommended for further evaluating dogs with vertebral instability [193]. Radiographic signs of the disease may not appear for several weeks after the onset of clinical signs. Hence, a radiographically normal spine does not preclude the diagnosis of diskospondylitis. Magnetic resonance imaging can be diagnostic prior to development of definitive radiographic abnormalities [194]. MRI findings in affected dogs have revealed increased T2 and decreased T1 signal intensity of the soft tissues ventral to vertebral bodies, the end plates of the same vertebral bodies and the intervertebral disk [195]. Blood and urine cultures should be obtained before starting antibiotic therapy. Reports of positive blood cultures range from 45% to 75% of affected dogs, while urine cultures can be positive in up to 50% of dogs [189,196]. In one report, fungal hyphae were identified in urine sediment from 6 dogs [181]. While serologic *Brucella* titers should be checked because of the public health significance, positive blood cultures are reportedly lower in dogs with *Brucella canis*-induced diskospondylitis [182]. Percutaneous aspiration of the infected vertebrae using fluoroscopy is a very useful diagnostic aid. In one study, positive bacterial cultures were obtained from 9 of 12 aspirated disk spaces including 2 dogs in which blood and urine cultures were negative [197].

Prognosis is usually favorable with aggressive long-term antibiotic therapy (e.g., from 2 to 4 months) if neurological signs are mild and the vertebrae are stable [198,199]. As a rule of thumb, until culture results are available, the organism should be assumed to be a *Staphylococcus*. The cephalosporins have been effective in the majority of small animal cases, e.g., cephalexin, at 22 mg/kg, PO, tid or cefazolin 20 mg/kg IV, qid for up to 5 days initially, if animals have fever or progressive neurological signs, followed by oral antibiotics. The following drugs have been recommended for treating diskospondylitis caused by other organisms [189,200,201]:



Microorganism	Antibiotic	Dose
beta-hemolytic <i>Streptococcus</i> sp.	Amoxicillin	20 mg/kg, PO sid
<i>Brucella canis</i>	Enrofloxacin Doxycycline Gentamycin	10 - 20 mg/kg PO sid 25 mg/kg PO sid 5 mg/kg IM or SQ sid
<i>Actinomyces</i> sp.	Penicillin G	100,000 U/kg IV, IM, or SQ qid
<i>Coccidioides immitis</i>	Ketoconazole Fluconazole	10 mg/kg PO bid (dog); 50 mg (total) PO bid or sid (cat) 5 mg/kg PO bid (dog); 25 - 50 mg(total) PO bid or sid (cat)
<i>Aspergillus</i> sp.	Amphotericin B (deoxycholate) Itraconazole	0.25 mg/kg IV every 48 hours until a cumulative dose of 8 - 12 mg/kg (dog) or 4 - 8 mg/kg (cat) is reached 5 mg/kg PO bid (dog and cat)

Prognosis for dogs with fungal diskospondylitis is guarded. In one report of 10 cases, 8 dogs were euthanized because of severe neurological signs, although one dog was alive after 4 years of continuous treatment with itraconazole [181]. Prognosis may also remain guarded in dogs with *Brucella canis* infection since serologic testing and radiographically active lesions may remain positive long after resolution of clinical signs [182]. Dogs with brucellosis should be neutered and clients advised of potential zoonotic infection. Vertebral curettage may expedite clinical resolution in cases refractory to medical treatment. In animals with severe neurological signs, spinal cord decompression and/or vertebral immobilization are indicated. In one report, surgical treatment involving distraction and stabilization to obtain intervertebral fusion was effective in treating lumbosacral instability caused by diskospondylitis [191]. Prognosis for surgically treated animals with severe neurological signs is often favorable [179]. Analgesics may also be required in some dogs because of pain. Recurrences may be common, especially in dogs with *Brucella canis* and in those with fungal infections, thereby necessitating re-treatment. The resolving lesion is characterized radiographically by cessation of the lytic process and by gradual replacement with new bone, sometimes causing fusion of the adjacent vertebrae. Radionuclide bone imaging, especially using gallium scans, may be a sensitive technique for confirming successful treatment [189]. Note that there is no apparent correlation between the ambulatory status and the ultimate outcome of dogs with diskospondylitis [193].

### Dural Ossification

Dural ossification is a degenerative disorder of dogs characterized by deposition of bone plaques on the inner surface of the dura mater [202-204]. Synonyms are osseous metaplasia of the dura mater and, incorrectly [205,206], ossifying pachymeningitis. These plaques occur in more than 60% of large and small breeds, of either gender, over 2 years of age and occur most often in the cervical region (e.g., C3 - T1) and lumbar (L1 - L6) areas of the spine [202,207]. Over 40% of 2 year old dogs had lesions in one report [202]. The etiology of this condition is unknown but seems unrelated to mechanical stress due to distribution of the changes [202]. Dural ossification is a common, incidental necropsy finding in dogs [203]. In extreme cases, the dura may be transformed into a solid bony tube[205]. The plaques often contain marrow cavities. The majority of plaques in one study were located ventrally while the remainder were found on dorsal and lateral aspects of the dural tube [202]. In general, dural ossification rarely causes clinical disease, but spinal cord compression with secondary degenerative changes in white and gray matter including edema, loss of neuronal cells, gliosis, and rarely, marked spinal cord compression with malacia have occasionally been reported in the dog [203,205]. Degenerative changes also may occur in nerve roots closely associated with the bony plaques [205]. Affected animals may be presented with a history of chronic paresis over several months, or tetraparesis, according to the location of the bony plaques, sometimes with atrophy of limb musculature and pain. Dural ossification is characterized radiographically (often as an incidental finding) by thin radiopaque linear shadows in cervical and lumbar areas, especially at the site of intervertebral foramina. The plaques sometimes may be confused with calcified herniated intervertebral disk material, vertebral osteophytes, or accessory processes on thoracic and lumbar segments [202]. They may be further defined using advanced imaging techniques, such as computed tomography [112].

If a definitive diagnosis is made in a dog with neurological signs, decompressive surgery may be attempted [202]. More common disorders should be given priority in the differential diagnosis of chronic spinal cord compression.

## Lumbosacral Stenosis

Stenosis (narrowing) of the vertebral canal and/or the intervertebral foramina in the lumbosacral area with compression of the nerve roots that form the cauda equina (L6 - 7 + S1 - 3 + coccygeal segments) and/or their related vasculature is an entity reported in dogs [208-211] and rarely, in cats [171]. This condition has been termed cauda equina syndrome, spondylolisthesis, lumbosacral instability, lumbar spinal stenosis, degenerative lumbosacral stenosis, and lumbosacral malarticulation and malformation. In most dogs, the spinal cord usually ends within the sixth or cranial half of the seventh lumbar vertebra, although in chondrodystrophoid and small-breed dogs the cord extends to the L7 - S1 level [86,212]. Most cases of acquired lumbosacral stenosis appear to be related to intervertebral disk degeneration at L7 - S1, especially Hansen type 2 protrusion (see disk disease) [211] with subsequent development of osteophytes at L7 - S1 endplates and articular facets, narrowing of the disk space at L7 - S1, subluxation of articular facets, thickening and in-folding of the normally taut interarcuate ligament, and thickened lamina and pedicles. The end result is degenerative stenosis with compression of the cauda equina. Lumbosacral instability, including dorsal dislocation of L7, has also been reported [213]. Morphometric studies suggest that multilevel congenital or developmental stenosis of the lumbosacral canal may contribute to acquired lumbosacral stenosis in large-breed dogs [214]. Other causes of acquired stenosis include diskospondylitis, neoplasia, and traumatic fracture/luxation of L7 - S1, sacrum, or the sacrococcygeal junction. Also, lumbosacral osteochondrosis, a developmental disturbance of the end plate of either the sacrum or L7 vertebra, with subsequent separation of an osteochondral flap, has been reported as a cause of lumbosacral stenosis in mature dogs [269-271]. This condition is often associated with disk disease, consequently, compressive lesions result from the flaps alone or in combination with disk material. An infrequently reported form of congenital ("idiopathic") stenosis in dogs occurs unassociated with disk disease. It is characterized by shortening of the pedicles, thickened and sclerotic apposition of the lamina and articular processes, in-folding and hypertrophy of the ligamentum flavum, and sclerotic and bulbous articular facets that bulge into the dorsal half of the canal, sometimes accompanied by malformations (e.g., hemivertebra, block vertebra, and transitional vertebra, such as lumbarization of S1 [215]. This congenital condition is thought to be associated with a developmental defect in the neural arch.

Acquired degenerative stenosis occurs most commonly in large breed dogs, many of which are highly trained or working dogs, including Border Collies [216-218]. German Shepherds are especially at risk for this degenerative disorder [219], possibly because of the presence of destabilizing transitional lumbosacral vertebral anomalies that predispose to premature disk degeneration [220]. The vertebral anomalies in the German Shepherd are considered to be inherited [221]. Smaller breed dogs appear to be more often affected by the congenital form of lumbosacral stenosis. In both forms, clinical signs are noted usually when dogs are mature to middle-aged (e.g., 5 to 8 years), possibly associated with age-related soft tissue and bony changes, along with altered spinal mechanics, resulting in cauda equina compression [222]. Males appear to be at higher risk than females in the acquired disease. In dogs with lumbosacral osteochondrosis, the mean age was 6.3 years, German Shepherds (56%), Boxers (11%) and Rottweilers (9%) were overrepresented, and the male:female ratio was 4:1 [271]. Irrespective of etiology, dogs with lumbosacral stenosis usually show varying signs of a lumbosacral syndrome depending on the level and extent of the lesion. Owners often note that affected dogs have difficulty rising or climbing stairs, and show signs of pain or stiffness during extensive physical activity [218]. Clinical signs may include pain (the most commonly reported sign) during direct palpation (especially downward pressure) of the lumbosacral area or during lumbosacral hyperextension, unilateral or bilateral pelvic limb paresis or lameness, proprioceptive deficits, tail paresis, hypotonia of anal sphincter with fecal incontinence, and urinary incontinence [211,216,222]. In some animals self-mutilation of pelvic limbs, tail, perineum, anal area, and genitalia may be noted. The occurrence of exercise-induced pain in some affected dogs, termed *neurogenic intermittent claudication* [222], may be related to dilatation of radicular vessels and subsequent compression of adjacent nerve roots in a stenotic region, e.g., intervertebral foramen or lateral recess of the caudal L7 vertebral foramen [223] narrowed by a degenerative process.

On plain films, indirect evidence of degenerative lumbosacral stenosis includes spondylosis deformans, disk space narrowing, and end-plate sclerosis. There may be evidence of lumbosacral fracture/luxation, osseous neoplasia, intradiskal osteomyelitis associated with diskospondylitis, or congenital lumbosacral stenosis. In dogs with lumbosacral osteochondrosis, a radiolucent defect occurs in the dorsal aspect of the affected end-plate along with one or more bone fragments in the vertebral canal and lipping, angling, and sclerosis of the dorsal part of the end-plate [271]. Stress radiography, such as dynamic flexion/extension studies, may accentuate the lumbosacral instability. Epidurography and diskography may provide useful information. In one study, combined survey radiography and discography-epidurography were correctly positive in 16 of 18 dogs (89%) [224]. Myelography has limited value in the evaluation of the cauda equina because the dural sac is elevated from the vertebral canal floor and often ends before the lumbosacral junction [225]. Computed tomography and MRI are probably the diagnostic procedures of choice [217,222,223,225-227], although findings of similar CT changes (but not vertebral subluxation) in the lumbosacral spine of older dogs without clinical disease may complicate diagnosis [112]. MRI can clearly reveal soft tissue, such as cauda equina, epidural fat, and intervertebral disk, at

the lumbosacral region without use of contrast medium [228]. MRI is also considered to give better information about the condition of the intervertebral disk (e.g., the hydration status of the nucleus pulposus) in dogs with degenerative lumbar spine diseases, than radiography [114]. CT scans also have an important diagnostic role. In a study evaluating canine lumbosacral stenosis using intravenous contrast-enhanced CT, the positive predictive values for compressive soft tissues involving the dorsal canal, ventral canal and lateral recesses were 83%, 100%, and 81% respectively [229]. However, no correlation was found between severity of the clinical signs and the severity of cauda equina compression as assessed by MRI in another study [277]. A gas-filled lumbosacral disk space (*vacuum disk* phenomenon) along with smaller gas bubbles in between the degenerated L5 - L6 dorsal articular facets (*vacuum facet* phenomenon) has also been revealed by CT in a 7 year old Rottweiler with cauda equina syndrome [230]. A diagnostic role for CT densitometry awaits further studies [283]. Electromyographic studies can demonstrate fibrillation potentials in lumbosacral paraspinal muscles, pelvic limbs, coccygeal muscles, and anal sphincter. In those cases where results of ancillary aids are equivocal, exploratory surgery may be the only means available for definitive diagnosis and treatment [222].

Grossly, marked compression and indentation of nerve roots may be seen, associated with stenotic lesions, bone fragments, disk material, inflammatory lesions, neoplasia, etc. Histological sections of samples removed from dogs with lumbosacral osteochondrosis revealed the osteochondral flaps consisted of a core of bone with or without a hyaline cartilage cap covering its margin, with the cartilage present consisting of a mixture of cartilaginous overgrowth and cartilage separation-necrosis [271]. I have commonly found extensive axonal degeneration characterized by linear rows of ovoids and balls, along with variable demyelination and remyelination in teased nerve fiber studies of biopsied nerve roots. In semithin sections, nerve fiber loss can be pronounced. Evidence of nerve regeneration may be seen in chronic lesions. In experimental studies in dogs, the involvement of intrinsic spinal cord neurons in the compression-induced cauda equina syndrome includes anterograde, retrograde and transneuronal degeneration in the lumbosacral segments [231] as well as marked changes in NADPH (nicotinamide adenine dinucleotide phosphate, reduced form) diaphorase-exhibiting and Fos-like immunoreactive neurons and heat-shock protein 72 (a cytoprotective protein whose expression is induced by a variety of harmful stimuli) [232].

Prognosis will depend on the underlying cause and the degree of damage to the nerve roots of the cauda equina. For congenital lumbosacral stenosis, prognosis is usually favorable with surgical decompression alone. Animals with acquired lumbosacral stenosis presenting with severe neurological deficits that include urinary or fecal incontinence have a guarded prognosis [222]. In dogs with less severe clinical signs, prognosis may be favorable when decompression by dorsal laminectomy is combined with foraminotomy and/or mass removal (e.g., disk, facets, ligaments, joint capsule, or osteophytes) [211,216,218,222,233]. In one report, dogs with lumbosacral osteochondrosis and instability treated with distraction-fusion along with dorsal laminectomy had a better prognosis than dogs without instability that were treated with dorsal laminectomy alone [271]. Medical treatment, such as rest, weight loss, anti-inflammatory or analgesic drugs, has usually been disappointing for congenital or acquired degenerative lumbosacral stenosis [222]. As for other acquired causes of lumbosacral stenosis, diskospondylitis can be successfully managed with antimicrobial therapy (see diskospondylitis), traumatic lumbosacral stenosis has a guarded prognosis (see spinal trauma), while lumbosacral neoplasia (see neoplasia) has a poor prognosis.

### Spinal Synovial Cysts

Extradural spinal synovial cysts originating from articular facet joint capsules and causing spinal cord compression have recently been described in dogs [109,234-237]. These cysts are characterized by a lining of single or multiple layers of flattened or cuboidal synovial cells with a wall composed of hypercellular synovium or fibrocollagenous tissue that may have cellular infiltrates (e.g., lymphocytes, plasma cells and macrophages) and focal areas of mineralisation or mucoid material. Another histological intraspinal articular facet joint cyst, called a ganglion cyst, is very similar to the synovial cysts but has no synovial lining. This form of cyst has also been recently reported involving L6 - L7 and L7 - S1 articular process joints in a 6 year old German Shepherd [238]. Adipose tissue and numerous capillaries were present on the outer surface of the cyst and foci of metaplastic cartilage were noted within the cyst wall. In humans, there is no clinical distinction between synovial and ganglion cysts of the spine that collectively have been termed "juxta-facet" cysts [239-244]. The pathophysiology of these cysts is uncertain, although they appear to develop secondary to osteoarthritis of the facet joints, e.g., synovial cysts arising from the synovial outpouchings through areas of weakened or destroyed capsular tissue; or ganglion cysts developing from mucinous degeneration of periarticular connective tissue [239,240]. In the canine cases reported to date, there has been no antecedent history of trauma or signs of vertebral instability. Furthermore, the cysts do not appear to be associated with concurrent degenerative structural disorders such as cervical spondylomyelopathy.

Preliminary data indicate that juxta-facet cysts in dogs occur most commonly in the cervical vertebrae, followed by thoracic vertebra, and least commonly in lumbar vertebrae. Dickinson and colleagues identified two groups [237]:

a) young (e.g., 12 - 36 months), giant breed dogs (e.g., Mastiffs and Great Danes) with multiple cysts involving one or more

levels of the cervical spinal cord usually affecting several vertebrae from C4 - C5 to C6 - C7; and b) older (e.g., 7 - 9 years), large breed dogs (including German Shorthaired Pointer and German Shepherds) with solitary cysts involving the thoracolumbar spinal cord and affecting vertebrae T13 - L1 or L1 - L2.

This classification seems appropriate since the 4 cases reported by Levitski and colleagues included 3 Mastiffs and a Great Dane aged between 15 and 18 months with variable cervical lesions from C3 - C4 to C6 - C7 associated with single or multiple cystic lesions [234]. The case reported by Flegel and colleagues also involved an 18 month old Great Dane with multiple cervical synovial cysts [235]. Consistent with the above-mentioned classification, the case report of an 8 year old Siberian Husky involved a single cyst located at the level of T13 - L1 vertebral level [236].

Clinical signs reflect location of spinal cord compression, e.g., cervical, cervicothoracic, thoracolumbar, or lumbosacral. Many dogs with cervical lesions show evidence of cervical pain [234]. The clinical course may be slowly progressive over several months. In one Great Dane, progressive ataxia and tetraparesis was noted over a 1 year period [237]. In the single case report to date on lumbar ganglion cysts in a 6 year old German Shepherd, the dog had a 6 month history of intermittent hind limb lameness, especially after exercise, difficulty handling stairs, and evidence of lumbosacral pain on hip extension and tail dorsiflexion [245]. Radiographic studies in dogs are usually unremarkable except for presence of degenerative arthritis of the facet joints and/or degenerative changes in intervertebral disks [234,237,238]. Lumbarization of S1 vertebra and fusion of the first caudal vertebra to the sacrum were present in the dog with multiple lumbar ganglion cysts [238]. Spinal cord compression has been demonstrated using myelography, usually with areas of axial deviation at sites of articular degeneration, and typically medial to the articulations [236,237]. In one report, a 1 by 2 cm cyst was found in the ventral epidural space associated with a pedicle attachment of the right T13 - L1 vertebral articular processes [236]. In a magnetic resonance imaging study, cysts appeared as well-defined circular defects, slightly hyperintense on post-contrast T1-weighted axial images and hyperintense on T2-weighted scans [234]. MRI revealed presence of multiple cysts arising from the L6 - L7 and L7 - S1 articular processes in one dog with lumbar lesions [245]. In addition to the presence of extradural transparent, fluid-filled cysts (typically 0.2 - 1 cm in size) usually adjacent to articular facets, surgical findings may include hypertrophic interarcuate ligaments, articular facets, and joint capsules [234].

Cerebrospinal fluid may be normal or characterized by mild to moderate protein increase ranging from 40 to 500 mg/dL, with normal cellularity or mild pleocytosis (usually mononuclear but sometimes with occasional neutrophils) [234,236,237].

Treatment by surgical decompression (e.g., hemilaminectomy or dorsal laminectomy) and removal of the cysts has usually resulted in satisfactory resolution of clinical signs and improvement in function postoperatively [234,236,237]. Vertebral stabilization using arthrodesis (lumbosacral) or a dynamic compression plate (thoracolumbar) has been performed in some dogs in addition to spinal cord decompression. Long-term prognosis appears to be good [234,236,237], although in one case, clinical recovery was incomplete following decompressive surgery [235]. To date, recurrence has been reported in one dog with a cervical lesion that improved with conservative treatment [237].

### **Spondylosis Deformans**

Spondylosis deformans is a degenerative, proliferative disease of the vertebral column characterized by the presence of vertebral osteophytes at intervertebral spaces, resulting in the formation of spurs or complete bony bridges [246,247]. Synonyms include spondylitis ossificans deformans, ankylosing spondylitis, spondylitis deformans, deformative ossifying spondylitis, spondyloarthritis, and spondylitis [246,247], all of which incorrectly imply the presence of inflammation [248]. Spondylosis deformans has been reported in dogs and cats, usually middle-aged, but some as early as 2 years of age. The incidence increases with age. Spondylosis occurs in about 50% of dogs by 6 years of age and 75% by 9 years [247]. It reportedly occurs in about 70% of asymptomatic domestic cats. A high incidence has been noted in the Boxer breed in which the condition is considered to be inherited [249]. In Boxers, dogs as young as one year of age may be affected, females are more often affected than males, and a positive correlation between hip dysplasia and spondylosis deformans has been noted [250,251]. In several comprehensive canine studies, Flat-coated Retrievers, Irish Setters, Bloodhounds, Rhodesian Ridgebacks, German Shepherds, Airedale Terriers, and Cocker Spaniels were identified as having a medium-high risk of spondylosis deformans, and females had a significantly higher incidence than males [246,252]. In dogs, vertebral sites most often affected were T9 - T10 and L7 - S1 in one study based on radiography of vertebral columns removed after death [246]. In some animals, the entire spine may be extensively involved [253]. Thoracic vertebrae are more commonly affected in cats [247].

While heritability appears to be a factor in some (perhaps all ?) of the high-susceptibility breeds [249], the underlying mechanisms responsible for spondylosis deformans remain unclear. It may be associated with degenerative changes in the annulus fibrosus of the intervertebral disks [246,254], particularly where the peripheral fibers of the annulus fibrosus (Sharpey's fibers) attach to the vertebral rim [247]. Interestingly, in an experimental collagenase chemonucleolysis study in cervical disks of normal dogs, spondylosis deformans developed at the sites of cervical enzyme injections [143], suggesting that trauma may be a predisposing factor in some instances (curiously, osteophytes did not develop in injected thoracic or

lumbar disks). Spondylosis deformans has been observed 1 - 4 years after intervertebral disk fenestration [255]. While spondylosis may occur secondary to disk degeneration/herniation (see cervical spondylomyelopathy), some consider the condition to be simply a manifestation of chronic degenerative disk disease, with bony spurs forming around diseased disks in an attempt to re-establish stability to the weakened disk spaces [246,254,256]. This view is not universally held (at least by me), especially since spondylosis deformans is uncommonly observed in chondrodystrophoid breeds predisposed to disk disease, such as Dachshunds and Poodles [246]. In one study involving 30 healthy Beagles [257], histological evidence of disk degeneration and changes in the mechanical properties of the intervertebral disk joint preceded radiographic changes of spondylosis. Karkkainen and colleagues, using magnetic resonance imaging, noted the presence of marked spondylosis deformans adjacent to intervertebral disks without evidence of disk degeneration [114]. Also, it is difficult to see a relationship between radiographic spondylosis deformans and disk degeneration in dogs one to two years of age [246,250,251]. While a radiographic study of a closed colony of Beagles (a chondrodystrophoid breed) did reveal the presence of spondylosis deformans that was age-related and located principally at low cervical, mid thoracic and cranial lumbar vertebral sites, these sites were somewhat different from the usual reports, and it is noteworthy that the lumbosacral site was minimally involved [258]. The role of spinal stress in spondylosis remains enigmatic. Some workers favor the idea that the sites most frequently involved represent those regions subjected to greatest mechanical stresses [256], while Morgan and colleagues state that normal or abnormal spinal motion, trauma, or areas of ligamentous attachment do not satisfactorily explain the variable frequency of lesions [246]. Lumbosacral osteophyte formation secondary to lumbosacral joint instability was considered as an unlikely event, based on quantitative lumbosacral angulation measurements [259]. Conversely, results of a recent radiographic study examining position and shape of osteophyte formations at canine vertebral endplates favored a role for mechanical factors in the pathogenesis of spondylosis deformans [260]. Anatomical dissection of the lumbosacral spinal columns from German Shepherds with spondylosis deformans revealed that diseased vertebrae have more flexibility than healthy vertebrae in the sagittal and frontal planes than but less so for dorsal flexion [261]. An imperfect L7 facet geometry may also predispose dogs, especially German Shepherds, to spondylosis deformans and may be influenced by congenital factors as well as body weight and locomotion in immature dogs [262]. Immunogenetic studies of Boxers failed to show any significant correlation between spondylosis deformans and leukocyte antigens and complement C4 allotypes [263]. Osteophytes tend to develop on ventral, lateral, or dorsolateral aspects of vertebral margins. Dorsally projecting osteophytes are rare. Classification based on extent of osteophytic proliferation has been proposed [246], ranging from small spurs projecting vertically from the vertebral body (grade 1), larger osteophytes with parrot's beak shape on both sides of the joint space (grade 2), osteophytic projection beneath the intervertebral space (grade 3), to extensive bridging of the intervertebral space resulting in bony fusion (grade 4). Osteophytic projections into the spinal canal, with compression of the spinal cord, is rare [264]. Similarly, osteophytic compression of spinal nerves at the level of the intervertebral foramina is infrequently encountered. In animals with spondylosis deformans, the disk space is usually of normal width [247,264]. Osteophytes seen after disk disease, with narrowing of the intervertebral spaces, tend to develop perpendicular to the vertebral body rather than bridge the disk space, and sclerosis may be seen in the vertebral end-plates [264].

In spite of the often dramatic radiographic changes, spondylosis deformans in dogs and cats tends to be a subclinical disorder, although stiffness, restricted motion, and pain might be attributed to spondylosis deformans in a small percentage of patients [247,265], sometimes in association with fracture of bony spurs or bridges. It is possible that subtle signs may be more easily detected in dogs required to be agile in work or sport [266]. Diagnosis is based on spinal radiography, with osteophytic presence often seen as incidental findings. Standard ventrodorsal and lateral radiographs without oblique views may miss many ventrolateral osteophytes [247,264]. Langeland and Stigen [267] found that oblique views contributed to a more exact localization of osteophytes, especially in the region of L6 - 7 and L7 - S1 where the intervertebral spaces are overlapped by the os ilium. In general, however, they considered that oblique views provided only minimal additional information for evaluating number and size of osteophytes. Advanced imaging, such as magnetic resonance imaging, may demonstrate evidence of nerve root impingement [227] and demonstrate soft tissue changes suggestive of degeneration of intervertebral disks, including loss of hydration of the nucleus pulposus [114]. Note that spondylosis deformans is commonly seen radiographically in dogs with degenerative lumbosacral stenosis [268]. Spondylosis deformans was also present in a 6 year old German Shepherd with intraspinal cysts (see spinal synovial cysts) of the L6 - L7 and L7 - S1 articular process joints along with lumbarization of the first sacral vertebra and fusion of the first caudal vertebra to the sacrum [238]. Treatment of spondylosis deformans is usually unnecessary. Nevertheless, analgesics can be given if spinal pain can be attributed to spondylosis deformans [265]. Surgery is only indicated in those rare instances in which both pain and neural deficit are present due to spinal cord or nerve root compression. Prognosis in animals with spondylosis deformans is usually very favorable.

### **Miscellaneous Disorders**

Several structural disorders, some of which are quite uncommon, may also be associated with compressive neurological

signs. These include **Chiari malformations**, **atlantoaxial subluxation**, and scoliosis/kyphosis/hemivertebrae/block vertebrae (see vertebral anomalies). These conditions are discussed in the chapter on Developmental Disorders. Skeletal abnormalities occasionally causing spinal cord and/or nerve root compression include mucopolysaccharidoses (see Mucopolysaccharidosis type VI), osteochondromatosis, hypervitaminosis A, and osteopenia-related spinal fractures and lordosis/kyphosis associated with nutritional secondary hyperparathyroidism. Compression of neural structures (spinal cord, brainstem, nerve roots) may be caused by a variety of mesenchymal and/or ectodermal cysts, including arachnoid cysts / intra-arachnoid cysts, and epidermoid and dermoid cysts (see malformation tumors). Cervical fibrotic stenosis (at C2 - C3 articulation) associated with yellow ligament proliferation, but without evidence of cervical instability, has been reported in an 18 month old neutered male Rottweiler [273]. Clinical signs were similar to those seen in dogs with cervical spondylomyelopathy. The stenosis was confirmed using myelography (no abnormalities were seen with survey radiography) and at surgery. Severe degeneration of the spinal cord affecting all funiculi and gray matter was found at the level of the yellow ligament compression. Identical myelographic and necropsy findings were observed by the authors in another young Rottweiler (15 months of age) presented for progressive ataxia. Acute and chronic spinal cord compression may occur from foreign bodies such as wood fragments secondary to oropharyngeal stick injuries [285,286].

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## Storage Disorders (4-Feb-2003)

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Storage diseases, or lysosomal enzymopathies are rare, degenerative disorders which, in the majority of cases result from a genetically-determined defect of a specific lysosomal acid hydrolase enzyme. There is subsequent accumulation and storage of substrate(s) within the cytoplasm of neurons throughout the nervous system, as well as in cells in other organs. Neurons are typically involved since they are post-mitotic, permanent cell populations [1]. Peripheral nerves are affected in some lysosomal enzymopathies. Most storage diseases have an autosomal recessive mode of inheritance, affect both males and female animals, have an onset early in life, manifest diffuse neurological dysfunction, and have a progressive, inexorable course, leading to death. These conditions tend to be infrequently seen in clinical practice and most published reports emanate from institutions where colonies are maintained for research as animal models of human disease. Lysosomal storage diseases in dogs and cats have been categorized as follows [1]:

### **Sphingolipidoses**

#### **Gangliosidosis**

#### **Globoid Leukodystrophy**

#### **Gaucher's Disease**

#### **Sphingomyelinosis (Niemann-Pick Disease)**

Niemann-Pick Disease Type A

- Phenotypic Variant of Niemann-Pick Disease Type A

Niemann-Pick Disease Type C

#### **Glycoproteinoses**

Fucosidosis

Mannosidosis

Galactosialidosis

#### **Mucopolysaccharidoses**

Mucopolysaccharidosis Type I

Mucopolysaccharidosis Type II

Mucopolysaccharidosis Type III A

Mucopolysaccharidosis Type III B

Mucopolysaccharidosis Type VI

Mucopolysaccharidosis Type VII

### **Mucopolipidoses**

I-cell Disease

#### **Miscellaneous**

Glycogenoses

- Glycogenosis Type Ia

- Glycogenosis Type II

- Glycogenosis Type III

- Glycogenosis Type IV

- Glycogenosis Type VII

Ceroid Lipofuscinosis

### **Ceroid Lipofuscinosis**

Ceroid lipofuscinosis (neuronal ceroid lipofuscinosis, or ceroidosis) is a putative neurodegenerative lysosomal storage disease associated with accumulation of lipofuscin and its related pigment, ceroid, in many organs, including neurons and glial cells of the CNS. The lipopigment complexes in ceroid lipofuscinosis and those reported with normal aging are biochemically different. Neuronal ceroid lipofuscinosis occurs as an autosomal recessive trait in English Setters [2], Tibetan Terriers [3,4], and Border Collies [5]. Males and females are affected. There have been sporadic case reports in a variety of breeds, including Chihuahua [6], Dachshund [7], Terrier-cross [8], Saluki [9], Corgi, as unpublished data, see [10], Japanese Retriever [11], Blue Heeler [12,13], Yugoslavian Sheepdog [14], Dalmatian [15], Cocker Spaniel [16-19], Poodle [20], Gordon Setter [21], Polish Owczarek Nizinny [22], and Miniature Schnauzer [23]. Ceroid lipofuscinosis has also been reported in cats [24-27].

The underlying pathogenesis remains unclear. In some forms of the disease in people, ceroid lipofuscinosis is considered to represent a lysosomal storage disorder characterized by the absence of a specific protease activity, e.g., a deficiency of pepstatin-insensitive acid proteases has been reported in classical late-infantile neuronal ceroid lipofuscinosis in children, but not in Tibetan Terriers, English Setters, or Border Collies with ceroid lipofuscinosis [28]. Some researchers suggest that this



neurodegenerative disease is associated with the disease process rather than storage of fluorescent lipopigment per se, and that the pathogenesis may involve mitochondria rather than a primary defect of lysosomal catabolism [29,30,267]. Lysosomal accumulation of subunit c of mitochondrial ATP synthase has been found in these three canine breeds, as well as in most forms of the disease in people [4,29,31]. Subunit c has also been identified in an affected cat [25]. Another class of neuronal ceroid lipofuscinosis is suggested by the finding of storage of sphingolipid activator proteins (SAPs) A and D, but not the c subunit, in affected Miniature Schnauzer dogs [32,33]. In people, five disease genes have been isolated [34]. Two of these (CLN1 and CLN2) encode lysosomal enzymes palmitoyl-protein thioesterase and tripeptidyl peptidase 1. The remaining three (CLN3, CLN5 and CLN8) encode putative membrane proteins of unknown function. A molecular genetic study on English Setters with ceroid lipofuscinosis did not indicate any linkage between the canine form of the disease and homologues of human CLN3 or CLN2 genes [35], and another study eliminated CLN3 as the locus for the disease in English Setters [36].

Clinical signs usually occur in young adult or mature animals between 1 and 9 years of age, although most animals are under 2 years of age. Signs are extremely variable but will usually include some form of abnormal behavior (e.g., aggression, depression, dullness, hyperactivity, loss of learned behavior, and acral mutilation) and visual impairment. These signs are often seen between 1 and 2 years of age. Other signs may include generalized ataxia, head tremors, seizures, and tetraparesis. Signs tend to slowly evolve over several years, especially in Tibetan Terriers [3], often with an accompanying loss of condition. The course in English Setters may be quicker with death within a year of initial signs [37]. The visual loss appears to be cortical, since, in contrast with human neuronal ceroid lipofuscinosis, severe retinopathy does not develop in most affected dogs [37-40]; however, retinal lesions appear to be more severe in Tibetan Terriers [4], in whom one of the early signs is nyctalopia (night blindness). Cocker Spaniels are clinically affected in adulthood and show progressive hind limb paresis, incoordination, and deficient postural reactions and proprioception [16]. Visual deficit is not a feature of the disease in the adult Dachshund [7,41].

Hematology, blood chemistries, urinalysis, CSF, and skull-spinal radiographs are normal, although autofluorescent sea-blue histiocytes have been described in bone marrow aspirates from affected English Setters [42]. Electrocardiographic changes have been reported in some affected dogs [43]. In contrast with early onset ceroid lipofuscinosis in English Setters, plasma carnitine concentrations are not decreased in the late-onset disorder in Tibetan Terriers [271]. Ophthalmoscopy may reveal a pigmented central retinal atrophy [16]. Early diagnosis of affected dogs has been reported with the use of quantitative ocular fundic autofluorescence [44]. Electroretinography has shown that the c-wave is typically either decreased in amplitude, lacking or replaced by a negative wave in English Setter dogs and Polish Owczarek Nizinny dogs with ceroid lipofuscinosis and associated damage of the retinal pigment epithelium [22]. These c-wave changes were seen early in the disease, when the a- and b-waves of the electroretinogram were still within normal limits. Computed tomography of the brain may show dilatation of the ventricles and atrophy of the cerebral cortex [45,46]. Since many cell types are affected by lipopigment accumulation, skin biopsies offer a useful antemortem diagnostic test [15].

Grossly, the cerebrum and/or cerebellum may be atrophic [1]. Microscopically, neuronal ceroid lipofuscinosis is characterized pathologically by distention of large and small neurons with fine granular storage material that stains gray to pale yellow with hematoxylin and eosin, bluish-black with Sudan Black and Luxol Fast Blue, orange with Sudan III, is periodic acid-Schiff (PAS) positive, and shows yellow autofluorescence with ultraviolet light. Affected neurons are distributed throughout the brain and spinal cord (including neurons of the peripheral nervous system), the intensity of which varies with the particular canine breed involved [1], e.g., Purkinje cell pigmentation is slight compared to that in large pyramidal cells of the cerebral cortex in Cocker Spaniels [16]. Loss of functional neuronal cytoplasm results from increasing pigment accumulation. Nerve cells may eventually die and disappear, with subsequent reactive astrogliosis [37]. This is especially evident in cerebellar Purkinje cells [1,3], although this was not observed in affected older Dachshunds [7]. In Cocker Spaniels, degenerative changes are reportedly more common in medulla and spinal cord [16,47]. Axonal spheroids occur in variable numbers throughout the brain and spinal cord [1,16]. Wallerian type degeneration may be seen, along with widespread swelling of astrocytes, and abundance of lipopigment-laden and vacuolated macrophages [3]. Histochemical and immunocytochemical methods have demonstrated abnormal neuronal mitochondria and loss of GABAergic neurons and synapses in cortex and cerebellum of affected English Setters [30]. Ultrastructurally, lipofuscin granules may appear as electron dense bodies with multilamellar profiles, bodies with fingerprint patterns, zebra crystalloids, or curvilinear profiles within neuronal membrane-bound cytosomes [9,13]. Macrophages tend to have more vacuolar cytosomes and less lipofuscin [1]. Storage inclusions may also be observed in retinal ganglion cells, autonomic ganglia, and cells in kidney, liver, pancreas, and smooth muscle fibers [18]. A distinct syndrome occurs in some Cocker spaniel dogs in which there is a generalized accumulation of a lipofuscin-like pigment with such a heavy accumulation in smooth muscle that the intestine and other organs have a brown discoloration [16-18]. In some cats, pigment deposition appears to be restricted to neural tissues [26]. Prognosis is guarded to poor. Attempts to treat the canine disease using allogeneic bone marrow transplantation have so far

been unsuccessful [48].

### **Fucosidosis**

Fucosidosis is a lysosomal storage disease resulting from a deficiency of the enzyme  $\alpha$ -L-fucosidase responsible for metabolism of glycoasparagines with terminal fucose residues [49]. As a consequence of this enzyme deficiency, there is an intralysosomal accumulation of substrate (fugoglycoproteins, oligosaccharides, and glycosaminoglycans) in various tissues including central nervous system (CNS), peripheral nervous system (PNS), kidney, pancreas, lymph nodes and lung. Fucosidosis occurs in English Springer Spaniels and has a worldwide distribution with reports from Australasia, the United Kingdom, and North America [50-54]. The disease is transmitted as an autosomal recessive trait [55].

Clinical signs are seen in young English Springer Spaniels and are characterized by progressive motor and mental deterioration. From 6 to 12 months of age, affected dogs may be anxious, apprehensive, and slow to learn. Ataxia, hypermetria, and proprioceptive deficits may be noted after 12 to 18 months [51]. Hearing, visual, and menace deficits may develop from 18 to 24 months, followed by severe incoordination over the next 6 months. During the third year of life, the bark frequently becomes monotonal and hoarse and dysphagia may be present, sometimes accompanied by regurgitation (although without evidence of megaesophagus). Most dogs over 24 months of age have episodic pendular nystagmus elicited by positional change of the head. Death is not uncommon in animals 3 to 4 years of age [54]. Enlarged ulnar nerves can be palpated in dogs with advanced disease. In Canada, a confirmed case of fucosidosis has been reported in a 10 month old English Springer Spaniel in which the initial problem was visual impairment [56]. Affected male dogs are infertile because of decreased total sperm output, low sperm motility, and morphologic abnormalities of the spermatozoa [57,58]. In contrast, affected females reproduce successfully, although estrus cycles are abnormal. Hematological studies indicate that up to 40% of lymphocytes have marked cytoplasmic vacuolation. Bone marrow macrophages show vacuolation also. CSF analysis is usually normal (WBC count, protein), although vacuolated mononuclear cells may be detected [54]. Clinically affected homozygotes have < 5% of normal enzyme activity in tissues, leukocytes, plasma, or cultured skin fibroblasts while carriers have approximately 50% of normal activity [54,55,59]. Motor and sensory nerve conduction studies are normal and no EMG abnormalities are present [54].

A notable gross autopsy finding is the pronounced enlargement of various nerves, associated with edema, fibroplasia, and aggregates of vacuolated endoneurial macrophages [1]. The cervical vagus is the most severely enlarged, sometimes measuring 10 mm in diameter [54]. Other involved nerves include optic, trigeminal, hypoglossal, glossopharyngeal, and spinal nerve roots, especially those supplying the brachial plexus. Dorsal root ganglia can also be enlarged. The lesions in the CNS are characterized by extensive cytoplasmic vacuolations and swelling of many neurons and supporting glia throughout the brain and spinal cord. Loss of neurons may be detected, especially of cerebellar Purkinje cells, and neurons in cuneate and gracile nuclei. Numerous vacuolated macrophages are found in the meninges. Axonal spheroids are frequently seen, especially in hypothalamic, cerebellar, cuneate, and gracile nuclei, usually associated with hypertrophic astrocytes [1]. Many phagocyte-like cells with a foamy, vacuolated, PAS-positive cytoplasm are present either free in the parenchyma or as pronounced cuffs around large vessels. Endoneurium and perineurium of peripheral nerves are infiltrated by foamy macrophages and nerve fibers are separated by edematous, finely fibrillar ground substance. There are minimal degenerative changes in peripheral nerves. Vacuolation is also found in cells of most visceral organs. Ultrastructurally, the vacuoles are seen either as membrane-bound, rounded cytosomes with an empty interior, or as amorphous, faintly stained material. Lectin staining of various paraffin-embedded tissues from human and canine fucosidosis has demonstrated a species-specific histochemical variability [60]. Unlike several other lysosomal storage diseases, Golgi staining of cortical pyramidal neurons in dogs with fucosidosis failed to demonstrate evidence of ectopic dendrite growth, although there is GM2-like immunoreactivity limited to glia and/or to non-pyramidal neurons [61].

Prognosis is guarded to poor. There is no treatment at present; however, treatment strategies in established colonies of dogs with fucosidosis are being assessed as a potential animal model for gene therapy and enzyme replacement therapy [62-71]. Bone marrow engraftment in dogs with fucosidosis has resulted in increased levels of alpha-L-fucosidase enzyme activity in leukocytes, plasma, and neural and visceral tissues, accompanied by a rapid improvement in the peripheral nerve and visceral lesions of fucosidosis and a more gradual improvement in the CNS pathology [72]. Long-term engraftment from an early age reduced the severity and slowed the progression of clinical neurological disease. In this study, transplantation after the onset of clinical signs was not effective.

The molecular defect underlying canine fucosidosis has been identified [73] and a polymerase-chain-reaction (PCR)-based diagnostic test for fucosidosis in English Springer Spaniels is now available, enabling detection of both carriers and homozygotes [71,74,75]. Using this screening test, fucosidosis can be controlled and ultimately eradicated from the English Springer Spaniel population [74].

## Galactosialidosis

An adult-onset lysosomal storage disorder has been reported in a 5 year old Schipperke dog with progressive cerebellar and central vestibular signs [76]. It is characterized by cerebellar atrophy with extensive loss of Purkinje and granular cells, and hydrocephalus. Enlarged and vacuolated neurons are observed in spinal cord, brain and autonomic ganglia. Ultrastructurally, enlarged secondary lysosomes filled with lamellated bodies are present in neurons and empty enlarged vacuoles are found in pancreatic centroacinar, ductal, and islet cells. Neurons stain with luxol fast blue, PAS, Concanavalina ensiformis agglutinin, and are autofluorescent. These findings are consistent with an accumulation of glycolipids containing terminal beta-galactosyl and alpha-sialyl residues, and N-linked oligosaccharides. Tissue activity of lysosomal beta-galactosidase was 50% of normal and the activity of beta-hexosaminidase was elevated. Brain lipid-bound sialic acid level was twice normal, with a small increase of GM1-ganglioside, but there was a significant elevation of GM2- and GM3-gangliosides. In addition, significant elevations of sialylated and non-sialylated oligosaccharides were noted. These clinical, biochemical and pathological findings are similar to those observed in human patients with adult-onset galactosialidosis.

## Gangliosidosis

Ganglioside storage diseases are inherited (autosomal recessive) defects of lysosomal hydrolase enzymes that result in accumulation of gangliosides (glycosphingolipids that are major constituents of plasma membranes in a variety of cells, especially neurons) and glycolipid substrates of these hydrolases within lysosomes of most neurons and glia throughout the nervous system [77-79], including brain, spinal cord, and autonomic ganglia.

In dogs and cats, several gangliosidoses have been identified and categorized according to the enzyme deficit and degree of visceral involvement. GM1 gangliosidosis has been reported in cats (Siamese, Korat, and Domestic Shorthair), and dogs (English Springer Spaniel, Portuguese Water dog, mixed-breed Beagle, Alaskan Huskies, Shiba, and cross-breed dogs) [77,79-93]. The accumulation of ganglioside in the brain is due to deficiency of acid  $\beta$ -galactosidase. In people, there are infantile (type 1), juvenile (type 2), and adult (type 3) variants of GM1. GM2 gangliosidosis has been reported in German Shorthair Pointers, Japanese Pointers, mixed-breed cats, and Korat cats [94-101]. Four major enzymatic variants of GM2 gangliosidosis are recognized in people based on their defective subunits or activator protein [100,101]:

- a. Type B, or Tay Sachs disease, due to deficiency of hexosaminidase A;
- b. Type O, or Sandoff's disease, due to deficiency of hexosaminidase A and B;
- c. Type AB, due to deficient or defective GM2 activator; and
- d. Type B<sup>-1</sup>, due to a mutation in the  $\alpha$ -subunit of  $\beta$ -hexosaminidase.

Massive accumulation of ganglioside occurs in all animals with GM2 gangliosidosis; however, the biochemical defect varies. A marked deficiency in activity of hexosaminidase A and B is reported in Korat cats (similar to Sandoff's disease in people). In the Japanese Spaniel, the biochemical basis is thought to be due to attenuation in stimulatory activity of the GM2 activator (similar to Type AB in people), and  $\beta$ -hexosaminidase activity may be 12 fold higher than that in normal brain [100]. In a report of GM2 gangliosidosis in a German Shorthair Pointer, massive accumulation of GM2 ganglioside was found in the brain and in other organs; however,  $\beta$ -hexosaminidase activity in plasma, liver, kidney and brain was normal, suggesting either an activator protein disorder or a B<sup>-1</sup> variant [101]. A partial deficiency of  $\beta$ -hexosaminidase activity has also been reported in this breed [99].

In most of the gangliosidoses, total ganglioside content of brain is high in clinically affected animals. Asialo (sialic acid free) derivatives of the gangliosides also accumulate in brain and liver [79]. High levels of other neutral glycosphingolipids may also be found. In some instances, different substrates are stored in neural and visceral tissues, probably reflecting the heterocatalytic activity of the deficient enzyme. For example, English Springer Spaniels and Portuguese Water dogs (PWDs) with GM1 gangliosidosis reportedly store GM1-ganglioside, asialo-GM1, and oligosaccharides in brain but only the PWDs store glycoproteins containing polylactosaminoglycans in visceral organs, and neither breed stores them in the brain [89]. Visceral storage of glycolipids and glycoproteins occurs in canine and feline GM1 gangliosidoses. Visceral involvement was not observed in the Japanese Spaniel with GM2 gangliosidosis [98], but in a report of GM2 gangliosidosis in a German Shorthair Pointer, storage of ganglioside was observed in liver, kidney, and spleen [101].

Clinical signs of GM1 gangliosidosis are first noted in dogs around 4 to 5 months of age and in cats from 2 to 5 months of age. In animals with GM2 gangliosidosis, onset of clinical signs is from 1 to 3 months of age in kittens, 6 to 12 months of age in German Shorthair Pointers, and around 18 months of age in Japanese Spaniels. Stunted growth and failure to eat may be noted early in life. Neurological signs are very similar in both species and are highlighted by their relentlessly progressive nature [79]. Cerebellar-like signs of ataxia-dysmetria, discrete head tremor, loss of balance, and abnormal nystagmus are often the first signs observed, followed by spastic paraplegia or tetraplegia, visual impairment, depression, sometimes dementia, seizures, aggression, and death. Corneal clouding has been seen in feline GM1 and GM2 gangliosidosis associated

with proteoglycan storage in corneal endothelial cells and fibroblasts [83,102]. Proportional dwarfism has been reported in English Springer Spaniel (these dogs also have coarse facial features, including ocular hypertelorism or increased width between the eyes), Portuguese Water dog, and Alaskan Husky puppies [90,103]. In addition, skeletal lesions such as deformed, irregular and abnormally widened intervertebral disk spaces, have been reported in English Springer Spaniels and Portuguese Water dogs [89]. Some cats with GM1 gangliosidosis manifest facial dysmorphism and hepatomegaly. Note that clinical signs in cats with panleukopenia (parvo) virus-induced cerebellar hypoplasia and the gangliosidoses are similar; however, cats with the former disorder typically show signs at birth or shortly thereafter and the signs remain relatively static. Several electrodiagnostic abnormalities have been reported in cats with GM1 gangliosidosis, including slow spinal evoked potentials in cats over 200 days of age and prolonged latencies of brainstem auditory evoked responses in cats over 90 days of age [104], findings consistent with the hypothesis that at least some of the abnormalities in cats with this lysosomal enzymopathy may be associated with altered CNS synaptic activity [105] (see also neurotransmission derangement, below). Motor and sensory nerve conduction velocities were normal and no abnormal spontaneous potentials were found by needle EMG [104].

Gross changes are usually not present although the liver may appear swollen and pale [1]. Microscopically, the storage material produces widespread neuronal distension (in CNS, autonomic ganglia, and retina) with a foamy to granular cytoplasm due to tightly packed vacuoles that displace the Nissl substance. Nuclei are eccentrically placed and there may be variable neuronal loss. Astrocytes may be similarly affected. Vacuoles in frozen sections often stain positively with Luxol fast blue and Grocott's method, PAS, and Sudan Black [1]. Axonal spheroids are variably seen in white matter in GM1 and GM2 gangliosidosis [106]. These structures may involve axons of inhibitory GABAergic neurons, suggesting that a resulting defect in neurotransmission in inhibitory circuits may be an important factor underlying brain dysfunction in animals with gangliosidosis [107]. Abnormal myelin development in the CNS (based on magnetic resonance imaging, white matter histopathology, and immunostaining) has been reported in dogs (English Springer Spaniel and Portuguese Water Dog) with GM1 gangliosidosis [108] and in cats with Sandhoff-like GM2 gangliosidosis [109]. In Alaskan Huskies with GM1 gangliosidosis, mild demyelination and axonal degeneration were accompanied by a significant astrogliosis in the gray matter and a significant loss of oligodendrocytes in the gray and white matters [90]. I have observed paranodal demyelination in up to 10% of single teased peripheral nerve fibers from some cats with GM2 gangliosidosis. Wallerian degeneration has also been reported in peripheral nerves, ventral and dorsal nerve roots, and in dorsal funiculi of all spinal cord segments in a 2 year old mixed breed dog with GM2 gangliosidosis (due to a presumed defect or deficiency of hexosaminidase activator protein) [257]. Ultrastructurally, cells are packed with membrane-bound vacuoles containing a membranous, lamellar material arranged in whorls, called membranous cytoplasmic bodies, or stacks of membranes in parallel arrays that have been termed zebra bodies [110]. The axonal spheroids are filled with electron-dense bodies, degenerating mitochondria, tubulovesicular profiles but little or no storage material [1]. Endothelial cells and perivascular macrophages in many organs are vacuolated in the gangliosidoses, including endoneurial macrophages in nerves from cats with GM2 gangliosidosis. The vacuoles tend to be empty or contain variable amounts of fibrillar or granular remnants of oligosaccharides which have been washed out during tissue fixation [1]. Golgi and ultrastructural studies reveal the presence of conspicuous enlargements (meganeurites - a manifestation of the storage process) located between the axon and cell body which appear to give rise to neurites and dendritic spines in cortical pyramidal neurons in canine and feline gangliosidoses [98,105,106,111]. These structures are postsynaptic to afferent fibers of unknown origin, are thought to contribute to neuronal dysfunction, and their distribution varies with cell type and brain region. The meganeurites are distended with membranous cytoplasmic bodies [111].

Skeletal lesions in English Springer Spaniel, Portuguese Water dog, and Alaskan Husky puppies are characterized by retarded endochondral ossification and osteoporosis [90,103]. Older puppies have focal cartilage necrosis within lumbar vertebral epiphyses. At the cellular level, lesions are characterized by chondrocytic hypertrophy and lysosomal accumulation of storage compounds. Premature thymic involution has been demonstrated in feline GM1 gangliosidosis [112]. In animals with peripheral nerve lesions, there may be slow motor nerve conduction velocities and reduced amplitude of evoked muscle potentials [257]. A tentative diagnosis is suggested by presence of cytoplasmic inclusions in peripheral blood leukocytes. In animals with GM1 gangliosidosis, oligosaccharides may be detected in urine in abnormally high quantities. Definitive diagnosis requires biochemical identification of the storage product and absence or marked reduction in activity (e.g., only 3 to 5% of the activity seen in homozygous normals) of specific lysosomal enzymes required for hydrolysis of accumulated compounds (e.g., chromatographic analyses may indicate a 5 to 10 fold increase in ganglioside storage). Note that the enzyme level in clinically unaffected heterozygotes is approximately 50% that of normal animals. Antemortem diagnosis can be made by enzyme assay of whole skin, cultured skin fibroblasts, liver, and purified leukocytes. Neonatal diagnosis using enzyme assays of placenta and umbilical cord has been reported in GM1 gangliosidosis [89]. Postmortem diagnosis is made most reliably by enzyme assay of brain. Prognosis is grave. There is no definitive treatment at present but

different strategies that have been tested in animal models include gene transfer and cell engraftment of neural stem cells engineered to express the specific enzyme deficiencies [113]. Allogeneic bone marrow transplantation early in life was found to be ineffective in canine GM1 gangliosidosis [114].

A suspected lysosomal storage disease has been reported in Abyssinian kittens in which the clinical signs are very similar to those reported above [115-118]. In human patients with gangliosidosis, peripheral nerve lesions are usually not significant, although motor neuronopathy tends to be common in late onset GM2 cases [258].

### **Gaucher's Disease**

Gaucher's disease, or glucocerebrosidosis, is a rare lysosomal storage disease caused by a deficiency of glucocerebrosidase (glucocerebroside  $\beta$ -glucosidase) that catalyzes the hydrolysis of glucocerebroside to ceramide and glucose [119]. A form of Gaucher's disease (similar to the type 2, infantile form in people) has been reported in Australian Silky Terriers [120-122]. Clinical signs reportedly occur around 4 to 6 months of age, are progressive, and are characterized by severe incoordination, wide-based stance, stiff gait, generalized tremors, hyperkinesia, and hypermetria. No gross findings have been noted in brain or spinal cord. Microscopically, the cytoplasm of many neurons in the brain, but not in the spinal cord, is distended and has a foamy, finely vacuolated appearance that often contains weakly eosinophilic, PAS-negative granules [122]. Nissl granules appear lost or peripherally displaced. Neurons of the dorsal and lateral thalamic nuclei and the dorsal hippocampus are especially affected, with less severe changes occurring in cerebral cortical gray matter, inferior colliculus, oculomotor nucleus, cochlear nucleus, trigeminal motor nucleus, superior olivary nucleus, dentate nucleus, fastigial nucleus, and ventral pontine gray matter. Gaucher cells (foamy, distended macrophages) are found in the cerebellar granule cell layer that may be mildly to severely atrophic. In addition to variable granule cell loss, degenerating Purkinje cells may be noted. At all levels of the brain there is mild to moderate spongy vacuolation of white matter and breakdown of myelin sheaths. The most severely affected areas include central white matter of the cerebral hemispheres, corpus callosum, optic tracts, cerebral peduncles, trapezoid body, central cerebellar white matter, and spinocerebellar and corticospinal tracts. Axonal spheroids may be seen, especially in ventral pontine gray matter. Gaucher cells are also found in several visceral organs, including liver (without signs of hepatomegaly) and lymph nodes. Ultrastructurally, the storage material in neuronal cytosomes appears laminated (zebra-like bodies) with variable fine fibrillar material. These structures, as well as twisted tubular material, are also seen in Gaucher cells.

Premortem diagnosis can be established by determining enzyme activity in leukocytes. Negligible  $\beta$ -glucosidase activity can be determined at pH 4.0 to 4.25 [123]. Postmortem diagnosis is made most reliably by enzyme assay of brain and liver as well as finding elevated levels of glucocerebroside, especially in liver [122]. Prognosis is poor. There is no treatment at this time.

### **Globoid Leukodystrophy**

Globoid cell leukodystrophy (Krabbe's disease or galactocerebrosidosis) is a rare lysosomal storage disease that results in progressive degeneration of white matter of the CNS and PNS. The disease is caused by mutations in the gene for the lysosomal enzyme galactosylceramidase (GALC) (or galactocerebroside  $\beta$ -galactosidase), which results in an accumulation of psychosine (galactosylsphingosine), a lipid that is highly toxic to oligodendrocytes and Schwann cells [124-127].

Globoid cell leukodystrophy is inherited as an autosomal recessive trait in young (3 to 6 month-old) West Highland White Terriers (WHWT) and Cairn Terriers [128-136]. The disease also has been reported in a 4 month old Beagle [137] a 2 year old Poodle [138], a 4 year old Basset Hound [139], 4 month old Blue Tick Hounds [140], two Pomeranians - 5 1/2 months and 14 years of age [139,141] and in Domestic Shorthair and Longhair kittens [142,270]. Recently, the condition has been reported in Irish Setter puppies around 6 weeks of age [143].

The clinical signs associated with this disease are variable and may reflect a multifocal syndrome. Animals often present with either signs of an ascending posterior paralysis or signs of a cerebellar syndrome, or both. Signs of a neuropathic syndrome are infrequently observed (e.g., in Irish Setters) and include depressed spinal reflexes, reduced muscle tone, and muscle atrophy. As the disease progresses, signs of a cerebral syndrome may be observed (including behavioral abnormalities, depressed mentation, visual deficits, etc.). In terminal cases, usually prior to 1 year of age, animals may become prostrate, demented, anorexic, and cachectic [134]. The progression of clinical signs appears more rapid in Irish Setters. Partial motor seizures characterized by repetitive jaw movements, muscle twitching, licking and chewing movements, fly biting and opisthotonus have been observed in some affected Irish Setters. Prolonged postrotatory nystagmus can be induced by rotating affected animals [144].

Results of ancillary aids usually are non-specific. Hematology, blood biochemistry, ophthalmology and spinal-skull radiography are normal. Analysis of CSF, however, can reveal an elevated protein level with cell counts usually within normal limits (albuminocytologic dissociation). Mononucleated or multinucleated PAS-positive cells are sometimes identified in CSF [145]. Magnetic resonance and magnetization transfer imaging in affected dogs are compatible with diffuse,

symmetrical white matter disease [146,147], while electrodiagnostic testing may reveal an abnormal brainstem auditory evoked response, abnormal spontaneous muscle activity (fibrillation potentials and positive sharp waves), and slow motor nerve conduction velocities [144,146]. Electroencephalographic traces also may be abnormal. Grossly, involved regions of fixed white matter of the CNS are gray and soft compared to normal white matter, while leukodystrophic peripheral nerves may appear normal or enlarged and whiter than normal nerves [134]. Ventricles may be enlarged 2 to 3 times normal size in some animals [148]. Significant lesions typically are confined to the white matter of the nervous system where any level of the brain and spinal cord may be affected, although lesions were limited to the brainstem and spinal cord in an older Basset Hound [139], and subcortical lesions were minimal in the affected Beagle [137]. Lesions tend to be symmetrical but with variable intensity at different levels within the neuraxis. In WHWT and Cairn Terriers, most severe changes may be seen in central and gyral white matter of the cerebrum, optic tracts, corpus callosum, fimbria, subcortical and adjacent folial white matter of the cerebellum, and outer one-half of the funiculi of the spinal cord [148]. The disease is characterized by destruction of white matter and replacement by aggregates (often in a perivascular fashion) of nonsudanophilic, nonmetachromatic, PAS-positive macrophages called "globoid cells", usually with accompanying hypertrophic astrocytes. Globoid cells are CD68 and ferritin positive, verifying their monocytic origin [270]. Myelin stains weakly in affected areas and there may be loss of oligodendrocytes. Axons are lost in the larger globoid cell collections. Changes in gray matter are minimal. In peripheral nerves, lesions may be typified by multifocal presence of segmental demyelination, variable axonal degeneration, and endoneurial accumulation of globoid macrophages [144,149,150]. In a recent study, a significant increase in the G-ratio (axon diameter divided by fiber diameter) was identified in affected dogs suggesting a decrease in total fiber diameter which appeared to be due to myelin loss or hypomyelination [144]. Ultrastructurally, intracytoplasmic vacuoles in Schwann cells and macrophages may contain myelin debris and characteristic twisted or straight-to-arched tubular inclusions [133]. Endoplasmic reticulum is often dilated and there may be evidence of mitochondrial degeneration [150].

Antemortem diagnosis may be suggested by nerve biopsy and demonstration of the characteristic ultrastructural inclusions [144,149,150] and established by levels of GALC activity in blood leukocytes of affected dogs or from cultured fibroblasts - the mean enzyme activity is reportedly 18% of the activity in normal dogs, whereas heterozygous carriers have a mean enzyme activity of about 50% of normal [151]. A screening test for clinically normal heterozygote carriers among WHWT and Cairn terriers, based on the molecular defect, has been established and provides rapid and accurate genotyping for all WHWT and Cairn terriers using any tissue sample available [152]. A similar DNA-based PCR test is available for Irish Setters [143]. Mutation analysis for carrier identification is superior to measurement of GALC activity because of the wide range of GALC values in peripheral blood leukocytes [127]. PCR testing will also facilitate prenatal diagnosis based on small fetal tissue samples (e.g., chorionic villus biopsy and amniotic fluid cells). Lipid analysis of brain reveals marked elevations in psychosine [127]. Deficient enzyme activity may also be found in liver and kidney [151].

Researchers and clinicians at the University of Pennsylvania, School of Veterinary Medicine, are investigating treatment strategies. To date, studies have shown successful transduction of cultured skin fibroblasts from an affected dog and normal canine bone marrow using a retroviral vector containing the human GALC cDNA [127]. However, intracerebral inoculation of an affected dog with transduced bone marrow stromal cells did not result in improved brain pathology (Dr. Charles Vite, personal communication, 2001).

## **Glycogenosis**

Glycogen storage diseases or glycogenoses, are uncommon disorders in dogs and cats. These diseases represent inborn errors of metabolism due to deficient activity of one of the enzymes involved in glycogen metabolism. The enzyme defects result in inadequate glycogen utilization and accumulation of glycogen of normal or abnormal chemical structure within various tissues, including muscle.

**Glycogenosis Type Ia** - a Von Gierke-like disease associated with glucose-6-phosphatase (G-6-Pase) deficiency has been reported in related Toy Breed puppies between 6 and 12 weeks of age [153], with signs of depression, coma, hypothermia, hypoglycemia, hepatomegaly and histological evidence of excessive glycogen accumulation in liver, kidney and sometimes myocardium, [154,155]. G-6-Pase deficiency has recently been reported in two 47-day-old littermate Maltese puppies presented for necropsy with a history of failure to thrive, mental depression, and poor body condition, [156] and the genetic mutation has been identified [157]. Gross findings included small body size and emaciation, severely enlarged pale livers, and pale kidneys. Histologically, there was marked diffuse vacuolation of hepatocytes with large amounts of glycogen and small amounts of lipid. Renal tubular epithelium was mildly to moderately vacuolated. Biochemical analysis showed that levels of G-6-Pase were markedly reduced in liver and kidney and that glycogen content was increased in liver. A colony has been established by crossbreeding Maltese and Beagle dogs carrying a mutated, defective G-6-Pase gene [158]. Puppies from this colony exhibited tremors, weakness, and neurologic signs when hypoglycemic. They had postnatal growth retardation

and progressive hepatomegaly. Biochemical abnormalities included fasting hypoglycemia, hyperlactacidemia, hypercholesterolemia, hypertriglyceridemia, and hyperuricemia. Microscopic and biochemical findings were similar to those found in the Maltese puppies [158]. Gene therapy has resulted in sustained G-6-Pase expression and improvement in liver histology and in biochemical parameters [266].

**Glycogenosis Type II** - or Pompe's disease in people, due to acid  $\alpha$ -glucosidase enzyme deficiency, has been reported in related Lapland dogs [154,159-161]. Clinical signs developed in animals after 6 months of age and were characterized by progressive muscle weakness, frequent vomiting and regurgitation, megaesophagus, dysphonia, persistent panting and cardiac abnormalities. Death occurred before the age of 2 years. Electromyographic studies revealed prolonged insertion activity, bizarre high frequency discharges, and occasional fibrillation potentials and positive sharp wave activity. The main lesions consisted of massive glycogen accumulation in membrane-bound vacuoles (glycogenosomes), involving most organs (including cerebral cortex and skeletal, cardiac, and smooth muscle) [160]. The disease has an autosomal recessive mode of inheritance [162] and may be confirmed by low leukocyte activity of acid  $\alpha$ -glucosidase. The enzyme protein is present in affected tissues, although in an inactive form [163]. Heterozygous animals may be identified by their partial deficiency of acid  $\alpha$ -glucosidase in leukocytes [162]. Prognosis is poor. There is no treatment.

**Glycogenosis Type III** - or limit dextrinosis, a glycogenosis similar to Cori's disease in people, is associated with a deficiency of the debranching enzyme amylo-1,6-glucosidase (reduced to between 0 and 7% of normal activity) and has been reported in German Shepherds and Akitas [164-167]. Muscular weakness and exercise intolerance was noted as early as 2 months of age. Other clinical signs included progressive abdominal distention as a result of hepatomegaly. Abnormal glycogen-like material occurred in liver, muscle (smooth, cardiac and skeletal) and neurons and glial cells of the CNS [154]. The stored substance lay freely dispersed in the cell cytoplasm without any indication of lysosomal storage [164]. The molecular basis for this disease has been characterized and a PCR screening test is available for diagnosis [259,260].

**Glycogenosis Type IV** - (Andersen disease, amylopectinosis), an inherited (autosomal recessive) deficiency of the glycogen branching enzyme  $\alpha$ -1,4-D-glucan:  $\alpha$ -1,4 glucan 6-glucosyl transferase, has been reported in a family of young Norwegian Forest cats [168,169]. Two cats developed fever, generalized muscle tremors, bunny-hopping gait, and weakness at 5 months of age which progressed to tetraplegia by 8 months of age. Fever disappeared at 8 months of age. Severe generalized muscle atrophy with contracture of the caudal antebrachial and cranial thigh muscles were present at the time 2 cats were euthanized (at 8 and 13 months). The older cat had ventricular hypertrophy. Abnormal fibrillation potentials were recorded in most muscles of one cat. The third cat died at 5 months of age before clinical signs developed. In another report, an unrelated Norwegian Forest cat had similar clinical signs beginning at 5 months of age [170]. In addition, this cat developed generalized, tonic-clonic seizures.

Microscopically, glycogen storage disease type IV is characterized by granular to globular intracytoplasmic storage of PAS-positive, diastase-resistant material that stains blue with hematoxylin and eosin and purple-blue with Lugol's iodine and is found in many organs, including skeletal muscle. Stored material was found in neurons throughout the CNS and PNS including dorsal and ventral horns, dorsal root ganglia, sensory and motor nuclei throughout the brainstem, Purkinje cells in the cerebellum, ganglion cells of the retina, autonomic ganglia, and myenteric plexi of the intestinal tract [168].

Accumulation of abnormal glycogen is accompanied by severe degeneration in the CNS and PNS, skeletal muscle, and heart. There is extensive loss of axons and myelin in peripheral nerves, spinal cord white matter, and cerebellar peduncles [171]. In peripheral ganglia and neurons within the CNS in which there is extensive storage, there is loss of neuronal cell bodies and astrogliosis. Ultrastructural evaluation of the stored material demonstrates irregular, non-membrane bound, finely granular cytoplasmic deposits [168,171]. Analysis of the glycogen in affected cats indicates less branching than normal and branching enzyme activity less than 10% of normal levels in liver and muscle [168]. Partial deficiency was found in muscle and leukocytes of the parents of affected cats. The molecular basis for this disease has been characterized and a PCR screening test is available for diagnosis [259,260].

**Glycogenosis Type VII** - an inherited (autosomal recessive) deficiency of phosphofructokinase (PFK), comparable to type VII glycogen storage disease in people, is recognized in English Springer Spaniels less than 12 months of age [172-175]. Muscle and erythrocyte PFK activities are deficient [174,175]. Characteristically, enzyme-deficient dogs have compensated hemolytic anemia and sporadic episodes of intravascular hemolysis with hemoglobinuria. Typically, clinical signs of muscle or CNS disease are not features of this disorder; however, muscle cramping has been noted in affected field trial dogs and in hunting dogs, both in the USA and in Europe [176,177]. Further studies are needed to determine if the behavioral abnormality observed sporadically in some affected dogs (called "Springer rage" syndrome by the breeders) is related to PFK deficiency. Interestingly, a severe, progressive myopathy characterized by weakness and muscle atrophy has been reported in an 11 year old PFK-deficient English Springer Spaniel [178]. Muscle changes included large accumulations of basophilic

floccular material in hematoxylin and eosin sections that stained strongly with PAS. Ultrastructurally, the non-membrane bound deposits were composed of short granular filaments, 8 to 12 nm in diameter and 100 to 160 nm in length, small granules, and amorphous material. Based on staining characteristics, the deposits were thought to represent an amylopectin-like polysaccharide with possible sialic acid residues. Total PFK activities were markedly reduced when assayed in skeletal muscles of this dog. In contrast with other PFK-deficient dogs, muscle glycogen in this animal was not increased above that of normal dogs [178].

A PCR-based diagnostic test has been developed for detecting dogs with PFK deficiency and clinically normal carriers [177,179]. Preliminary treatment attempts using bone marrow transplantation have shown promise. An identical condition, having the same molecular mutation, has been found in American Cocker Spaniels [180]. Screening for PFK deficiency is recommended for English Springer Spaniels with suspicious clinical signs and before using any for field trials or breeding in order to prevent the further spread of this hereditary disorder [177].

A suspected glycogen storage disease that was accompanied by growth retardation, progressive muscular weakness, atrophy of pelvic limbs, and death has been reported in cats between 1 and 4 months of age [181]. There was hepatomegaly, splenomegaly, and focal necrosis of muscle and elevated serum creatine kinase and aldolase activity. Glycogen-like material occurred in reticuloendothelial cells, liver and muscle cells.

### **Mucopolidoses**

**I-cell Disease** - I-cell disease is a rare lysosomal storage disease caused by a deficiency of the enzyme N-acetylglucosamine-1-phosphotransferase (GlcNAc-phosphotransferase) recently reported in cats [261,262] and considered homologous to I-cell disease (or mucopolidosis type 3) in humans [199]. The disease is characterized by facial dysmorphism, large paws in relation to body size, dysostosis multiplex, and poor growth. Affected cats appear dull, ataxic, and may have decreased muscle tone. Radiographic abnormalities are seen as early as 2 weeks of age and lesions include long bone metaphyseal flaring, radial bowing, and antebrachial-carpal joint luxation. Fusion of cervical and lumbar vertebral bodies develop within the first 5 months of life. In some severely affected cats, spina bifida and hemivertebrae have been noted. Retinal degeneration may be detected around 2 - 3 months of age. The condition has an autosomal recessive mode of inheritance and affected cats either die or require euthanasia within 1 day to 7 months of age. The urine mucopolysaccharide spot test is negative. The enzyme GlcNAc-phosphotransferase is deficient in leukocytes and cultured fibroblasts. Inclusion bodies have been detected in cultured fibroblasts but not in white blood cells. Inclusions have also been seen in endothelial cells and chondrocytes. Storage lysosomes contained oligosaccharides, mucopolysaccharides, and lipids. Tissues most affected are bones, cartilage, skin, and other connective tissues. Parenchymal cells of liver and kidney are unaffected, as is skeletal muscle. Few cerebral cortical neurons show lipid inclusions and peripheral nerves appear normal. It should be noted that the subtle neurologic signs in affected cats are believed to be secondary to the orthopedic changes [262].

### **Mannosidosis**

Mannosidosis is a lysosomal storage disease resulting from a deficiency of the enzyme alpha-D-mannosidase in various organs, including brain, kidney and liver. Lysosomal alpha-D-mannosidase is involved in the catabolism of N-linked glycoproteins through the sequential degradation of high-mannose, hybrid, and complex oligosaccharides [182]. In feline alpha-mannosidosis, the accumulated oligosaccharides primarily represent intact oligomannosyl moieties of N-linked glycans rather than the products of residual alpha-mannosidase activity [183]. As a consequence of this enzyme deficiency, there is intralysosomal accumulation of glycoprotein-derived, mannose-rich oligosaccharides. This rare disease has been reported in a 7 month old Domestic Shorthair (DSH) cat [184,185], in Domestic Longhaired (DLH) cats aged between 7 and 15 months [186], and in Persian kittens [187-189]. There is considerable heterogeneity among these reports regarding clinical onset, clinical course, and pathology. All cats have signs of apparent cerebellar dysfunction, including ataxia-dysmetria and intention tremors. However, stillbirths and neonatal deaths may occur in Persian litters and many affected animals may not survive the first 6 months of life [189]. Some affected cats show gingival hyperplasia, bizarre behavior, such as running in circles, jumping without provocation, and standing in the water bowl, and progressive dementia and apathy [187]. Other findings include corneal changes, open suture lines in calvaria, thymic aplasia, hepatomegaly, and polycystic kidneys. In the DSH cat, thoracic limb deformation due to lateral dysplasia of the carpus was noted at 4 months of age [184]. Other findings included radiographic abnormalities of the spine and long bones, cataracts and tapetal changes, hepatomegaly, lymphadenopathy, and thickened peripheral nerves. In DLH cats, additional clinical signs such as lurching, falling, opisthotonus, paraplegia, megaesophagus and systolic heart murmur have been reported; however, none had evidence of hepatomegaly, skeletal deformities or ocular abnormalities [186].

Microscopic lesions are characterized by extensive vacuolation of neurons and glial cells of the nervous system (more in astrocytes than oligodendrocytes), as well as in spinal and enteric ganglia [186]. Numerous vacuolated macrophages may be seen in peripheral nerves and in perivascular spaces of the CNS, and in a variety of parenchymal organs. Poor myelination of the cerebral white matter (especially in the corona radiata) and axonal spheroid formation (torpedoes, neuroaxonal dystrophy)



in cerebral and cerebellar white matter, thalamic radiations, and cerebellar roof nuclei have been observed in Persian kittens, while abnormally thin myelin was noted in DSH cats. Neither these changes nor the extensive vacuolation of hepatocytes and pancreatic acinar cells seen in Persian and DSH cats, were observed in the DLH cats [186], although abundant axonal spheroids were found ultrastructurally in DLH cats. Immunocytochemical studies showed that the spheroids reacted positively with glutamic acid decarboxylase, the synthetic enzyme for the inhibitory neurotransmitter, gamma-aminobutyric acid [107]. Extensive Purkinje cell loss was seen only in the DLH cats. In all cats, ultrastructural findings indicate that most neurons contain empty membrane-bound vacuoles or only small amounts of finely granular material. Some neuronal cytosomes have linear membranous profiles and vesicular or lamellar, membranous cytoplasmic bodies [184,186]. Lipofuscin-like inclusions may be seen in larger neurons. Vacuoles are present in CNS vascular endothelial cells and pericytes. Neuritogenesis, as determined by Golgi staining, is not as prominent in cortical neurons of mannosidosis cats as it is in other storage disorders, such as gangliosidosis, sphingomyelinosis, and mucopolysaccharidosis; however, meganeurites, secondary neurite formation, and various types of dendritic changes have been observed [190]. Very similar changes have been reported in swainsonine-induced feline  $\alpha$ -mannosidosis [191].

Diagnosis is based on demonstrating a deficiency of acidic  $\alpha$ -mannosidase in brain, liver or kidney, or detecting mannose-rich oligosaccharides in urine [192]. A three-fold increase in the level of alpha-D-mannoside has been reported in liver and brain of affected cats [193]. Lectin histochemistry on formalin-fixed, paraffin-embedded tissue sections is also a simple, reliable method for diagnosing alpha-mannosidosis [194]. Cytoplasmic vacuolation is seen in blood lymphocytes and monocytes in Giemsa-stained blood smears [188]. It is possible to distinguish between heterozygous and affected kittens by using enzyme assay and oligosaccharide determination in placenta:  $\alpha$ -mannosidase activity is  $< 10\%$  of control in affected kittens, and  $< 50\%$  in heterozygous kittens [195]. Prognosis is poor. Treatment strategies are being investigated in colonies of affected cats. The cDNA encoding lysosomal alpha-mannosidase has been cloned in the Persian cat, and not surprisingly, in accordance with the variable clinical and pathological features, genetic studies have shown there is molecular heterogeneity for feline alpha-mannosidosis [196]. Researchers at the University of Pennsylvania, School of Veterinary Medicine, have also reported that retrovirus vector transfer of a new human alpha-mannosidase cDNA resulted in high-level expression of alpha-mannosidase enzymatic activity in deficient human and feline fibroblasts [197]. In a recent study by this group using Persian crossbred cats with a four base pair deletion in the gene encoding alpha-mannosidase [198], there was evidence of defective myelination in both CNS and PNS. Magnetic resonance imaging of the brains of affected cats revealed diffuse white matter signal abnormalities throughout the brain. Quantitative magnetization transfer imaging showed a 8 - 16% decrease in the magnetization transfer ratio in the white matter of affected cats compared to normal cats indicating myelin abnormalities. Histology confirmed myelin loss throughout the cerebrum and cerebellum. Affected cats showed slow motor nerve conduction velocity and increased F-wave latency. Single nerve fiber teasing revealed significant demyelination-remyelination in peripheral nerves. Ultrastructural findings in peripheral nerves included presence of numerous membrane-bound vacuoles within Schwann cell cytoplasm, endoneurial and perineurial macrophages, endothelial cells, and pericytes. The cytosomes were either empty or contained a fine fibrillar material. Many myelinated fibers were thinly myelinated and there was scattered presence of onion-bulbs and naked axons [198]. A significant increase in the G-ratio (axon diameter divided by fiber diameter) was identified in affected cats suggesting a decrease in total fiber diameter associated with myelin loss and/or hypomyelination.

### **Mucopolysaccharidoses**

The mucopolysaccharidoses are a diverse group of inherited lysosomal diseases that result from deficits in the metabolism of certain glycosaminoglycans or acidic mucopolysaccharides, such as dermatan, heparan, chondroitin, and keratan sulfates, which accumulate in various connective tissues, as well as in brain, and are excessively excreted in urine. Thirteen subclasses of mucopolysaccharidosis have been described in people [199]. Clinically these diseases are characterized by multisystem abnormalities including skeletal alterations (e.g., facial dysmorphism), limited joint mobility, corneal clouding, hepatosplenomegaly, and mental retardation. Similar signs have been seen in dogs and cats, but usually without neurological involvement, despite accumulation of incompletely degraded glycosaminoglycans in the CNS. The mucopolysaccharidoses described in cats and dogs are considered to be recessively inherited.

**Mucopolysaccharidosis Type I (MPS I)** - caused by a deficiency of alpha-L-iduronidase, has been reported in Domestic Shorthair cats less than 6 months of age [200]. Signs include lameness, broad face with depressed nasal bridge and frontal bossing, small ears, corneal clouding, and multiple bone dysplasia, including fusion of vertebrae over the cervicothoracic junction, pectus excavatum, and bilateral coxofemoral subluxation. Neurological signs are usually not seen or mild, however exaggerated myotatic reflexes, impaired pelvic limb proprioception, along with reduced cervical mobility range and apparent pain on cervical palpation have been recently described suggesting possible cervical myelopathy [265]. Slowing of CNS conduction, predominantly in the cervical spinal cord, as determined by somatosensory evoked potentials, is supportive of

some form of cervical cord dysfunction in affected cats [265]. Cats excrete excessive amounts of glycosaminoglycans in urine, and glycosaminoglycan storage is evident in fibroblasts and neurons. Gross postmortem findings include hepatosplenomegaly, opaque meninges, and lateral ventriculomegaly. Membrane-bound vacuoles, either empty or containing a fibrillar material or lamellar cytoplasmic inclusions (zebra-like bodies) are present in CNS neurons, hepatocytes, chondrocytes, vascular and splenic smooth muscle cells, bone marrow leukocytes, and fibroblasts of the skin, eye, and cardiac valves [201]. Activity of alpha-L-iduronidase is deficient, e.g., approximately 5% of that of control cats in cultured fibroblasts and leukocytes [202]. An ill-defined relationship between MPS I and meningiomas has been reported in young cats less than 3 years of age [203]. Enzyme replacement therapy (recombinant alpha-L-iduronidase) was effective in reversing storage in some tissues at the biochemical and histological level in MPS I cats, although the enzyme was not consistently detected in cerebral cortex, brainstem, or cerebellum and the histological appearance and ganglioside profiles did not improve [204]. The mutation causing MPS I in cats has been identified and characterized [205]. Feline MPS I resembles Hurler's disease in people.

In dogs, a similar enzyme deficiency has been noted in Plott Hounds [206,207], which more closely matches Hurler-Scheie syndrome in people, a form of alpha-L-iduronidase deficiency of intermediate severity [207]. Clinical signs are seen in dogs less than 6 months of age, and are similar to those seen in cats with MPS I: corneal clouding, abnormal facies, impaired mobility, pain upon handling, stunted growth, joint stiffness, cardiac changes, and hepatosplenomegaly. Neurons at all levels of the CNS have varying degrees of cytoplasmic vacuolation, but neuronal loss or necrosis is not appreciable. There is vacuolation of perivascular mononuclear cells in the CNS, and leptomeninges are thickened and hypercellular [208]. Ultrastructural findings are similar to those seen in affected cats with both empty membrane-bound vacuoles and lamellar structures resembling zebra bodies. Cytoplasmic vacuolation, usually involving fibroblasts or fixed tissue macrophages, occurs in most extraneural tissues. Activity of alpha-L-iduronidase in the dogs is profoundly deficient (from 0 - 1% of the control mean values) in cultured fibroblasts and leukocytes [207]. Reduced levels of brain beta-galactosidase and increased levels of brain beta-hexosaminidase have been reported [208]. Increased amounts of dermatan sulfate and heparin sulfate are found in brain and many extraneural tissues (especially in liver) [208] and these glycosaminoglycans are excreted in urine. While Golgi impregnation studies in feline MPS I reveal that cortical pyramidal neurons may have axon hillock enlargements (meganeurites) and/or ectopic secondary neuritic processes, aspiny meganeurites without ectopic neurite growth have been reported in the canine disorder [209]. Fluorometric assays of alpha-L-iduronidase in serum are available for identifying affected, carrier, and normal dogs [210]. Allogenic bone marrow transplantation reportedly diminishes MPS I-related lesions in affected dogs [211,212]. In contrast, hematopoietic stem cell gene therapy has not produced clinical improvement in dogs [213,214].

**Mucopolysaccharidosis Type II (MPS II)** - or Hunter syndrome, has recently been reported in a 5 year old male Labrador Retriever with signs of progressive incoordination, visual impairment, and exercise intolerance [215]. Coarse facial features, macrodactylia, unilateral corneal dystrophy, generalized osteopenia, progressive neurologic deterioration, and a positive urine spot test for acid mucopolysaccharides suggested mucopolysaccharidosis. Intracytoplasmic vacuoles were most prevalent in epithelial cells, endothelial cells, and histiocytes of liver, kidney, thyroid gland, and spleen. Ultrastructural examination disclosed electron-lucent floccular or lamellar membrane-bound storage material characteristic of mucopolysaccharides. PAS-positive intracytoplasmic material was identified in multiple neurons in the medulla, pontine nucleus, cerebellum, and spinal gray matter horns. Biochemical assays identified a deficiency in iduronate-2-sulfatase (IDS) activity in cultured dermal fibroblasts compared with normal dogs. Hair root analysis for IDS showed that the dam was a carrier of X-linked Hunter syndrome and that a phenotypically normal male littermate of the affected dog was normal.

**Mucopolysaccharidosis Type III A (MPS III A)** - associated with a deficiency of the lysosomal enzyme heparan sulfate sulfamidase, has been reported in adult Wire-haired Dachshunds [216,217], and more recently, in New Zealand Huntaway dogs [273]. Around 3 years of age, dogs develop progressive neurological signs of ataxia and intention tremor. Dysuria may be seen late in the condition. Mentation remains normal throughout the course of the disease, which may extend over several years. A mucopolysaccharide storage is indicated by positive toluidine blue spot tests of urine. The diagnosis of MPS III A is confirmed by documentation of urinary excretion and tissue accumulation of heparan sulfate and decreased sulfamidase activity in fibroblasts and hepatic tissue. Mild cerebral cortical atrophy and dilation of the lateral ventricles may be grossly evident. Light microscopically, fibroblasts, hepatocytes, and renal tubular epithelial cells are vacuolated. Within the nervous system, cerebellar Purkinje cells, neurons of brainstem nuclei, ventral and dorsal horns, and dorsal ganglia are distended with brightly autofluorescent, PAS-positive, and sudanophilic material. Vacuolated macrophages may be seen in the meninges. Ultrastructurally, visceral storage presents as membrane-bound vacuoles with finely granular, variably electron-lucent contents. Neuronal storage appears as membranous concentric whorls, lamellated parallel membrane stacks, or electron-dense lipid-like globules. In one dog, additional lesions included calcium oxalate uroliths, severe secondary calcification of tissues including the brain, and storage deposits in some neurons [217]. This condition is being studied as a model of Sanfilippo

syndrome type A in people. The molecular defect has been identified in both canine breeds [218,273].

**Mucopolysaccharidosis Type III B (MPS III B)** - or Sanfilippo B syndrome, has recently been reported in Schipperke dogs in which pedigree analysis supported an autosomal recessive mode of inheritance [219,263]. In this report, clinical signs were seen in male and female Schipperkes around 3 years of age that were characterized by pelvic limb ataxia-dysmetria, wide-based stance, truncal swaying, occasional stumbling and falling, fine head intention tremor, and whole body tremor. The menace reaction was absent although pupillary light reflexes were normal, and peripheral retinal degeneration was noted. The condition was slowly progressive over several years. Granules in mononuclear blood cells stained positively with toluidine blue. The urinary mucopolysaccharidosis spot test was positive due to presence of heparan sulfate. Pathological findings revealed marked cerebellar atrophy, Purkinje cell loss, and neuronal and hepatic storage material that stained positively with toluidine blue and PAS. Activity of N-acetyl- $\alpha$ -D-glucosaminidase was <5% of normal. Other measured lysosomal enzyme activities were elevated. Note that the clinical signs described are similar to those seen in a 5 year old Schipperke with adult-onset galactosialidosis [76].

**Mucopolysaccharidosis Type VI (MPS VI)** - or Maroteaux-Lamy syndrome, has been reported in 2 to 3 month old Siamese cats [220], and recently in a 3 year old Siamese/shorthaired European cat [272]. This disorder, transmitted as an autosomal recessive trait, is caused by a deficiency of the enzyme arylsulfatase B (N-acetylgalactosamine-4-sulfatase) [221]. The clinical features of affected animals include small head, flat, broad facies, wide-spaced eyes, depressed bridge of the nose, corneal clouding, small ears, large forepaws, and a concave deformity of the sternum [222]. These signs are almost identical to cats with MPS I; however, Siamese cats have long bone epiphyseal dysplasia and toluidine blue-positive granules in circulating neutrophils. Signs of intracranial disease are usually not seen, although seizures have also been reported in a 2 year old Siamese cat with MPS VI [223]. Additional radiographic findings in Siamese cats may include long bone exostoses, severe spondylosis, severe osteoarthritis of the articular facets of the entire spine, pectus excavatum, hypoplasia and fragmentation or abnormal ossification of the dens, and aplasia or hypoplasia of frontal and sphenoid sinuses. Hepatosplenomegaly is not a prominent feature [224]. Membrane-bound cytoplasmic inclusions have been noted in hepatocytes, bone marrow, granulocytes, vascular smooth muscle cells, and fibroblasts in skin, cornea, and cardiac valves. Lesions in CNS are reportedly restricted to mild ventricular dilatation, and perithelial cell vacuolation in the connective tissue of the meninges and choroid plexus, with membrane-bound inclusions in the cytoplasm of perivascular cells of the brain and spinal cord [224]. Neurons and glial cells are unaffected. It has been estimated that approximately 25% of immature cats with MPS VI develop clinical signs of a thoracolumbar syndrome secondary to cord compression from focal bony protrusions into the vertebral canal [222]. Signs are characterized by varying degrees of pelvic limb paresis that may progress to paraplegia, incontinence and depressed pain sensation caudal to the level of the thoracolumbar lesion. Spinal cord compression can be confirmed with myelography. Microscopic changes in the cord include myelin loss, Wallerian degeneration, astrocytosis, neuronal dropout, and neovascularization. Affected cats with MPS VI excrete excess dermatan sulfate in the urine. Arylsulfatase B activity is less than 10% of normal in affected homozygous cats and 50% lower than normal in asymptomatic obligate heterozygous cats. Prognosis can be favorable in cats manifesting spinal cord signs with surgical decompression early in the course of the disease. The genetic mutation of this disorder has been identified and a rapid PCR-based screening method to genotype individuals has been developed [225]. It has been reported that two mutations within a feline mucopolysaccharidosis type VI colony cause three different clinical phenotypes [226]. Allogenic bone marrow transplantation can produce significant and sustained clinical and biochemical improvement in cats with MPS VI [227]. Resolution of corneal clouding and improvement in facial dysmorphism, walking ability, and better coat condition were reported, together with leukocyte arylsulfatase B activity and urinary dermatan sulfate excretion returning to normal. Enzyme replacement therapy in the MPS VI cat is also effective at reducing or eliminating pathology in most connective tissues, including bone development [228,229]. In one study, enzyme replacement therapy (recombinant feline N-acetylgalactosamine-4-sulfatase administered at a dose of 1 mg/kg of body weight), altered the clinical course of the disease in two affected cats treated from birth [230]. After 170 days of therapy, both cats were physically indistinguishable from normal cats with the exception of mild corneal clouding. MPS VI has also been reported in several canine breeds, including Miniature Pinschers, Miniature Schnauzers, Chesapeake Bay Retrievers and Corgis [231,264] with clinical, radiographic, and biochemical findings similar to those seen in affected Siamese cats. Levels of both dermatan sulfate and chondroitin sulfate were increased in urine. Activity of arylsulfatase B was less than 1% of control values. The genetic mutation of this disorder has been identified and a DNA test is now available to distinguish between normal, carrier and affected animals [264].

**Mucopolysaccharidosis Type VII (MPS VII)** - associated with beta-glucuronidase deficiency has been reported in a dog, the offspring of a father-daughter mating [232]. Pelvic limb weakness was evident at 8 weeks of age and became progressively worse. The dog had a large head, a shortened maxilla, and corneal granularities. Most joints were extremely lax

and easily subluxated, with joint capsules that were swollen and fluctuant. The dog was alert and had apparently normal pain perception. No neurological signs were noted. At 13 months of age, there was radiographic evidence of extensive skeletal disease. The electrophoretic pattern of precipitated glycosaminoglycans indicated a predominance of chondroitin sulfate. The animal died suddenly from gastric dilatation. There was generalized hepatomegaly, thickening of the atrioventricular heart valves, and generalized polyarthropathy. Vacuolated cytoplasm was observed in hepatocytes, keratocytes, fibroblasts, chondrocytes and cells of the synovial membrane, retinal pigment epithelium, and cardiac valves. Neurons had cytoplasmic vacuoles. Electron microscopy demonstrated membrane-bound cytoplasmic inclusions in polymorphonuclear leukocytes, hepatocytes, synovium, heart valves and spleen. Levels of chondroitin sulphates were increased in urine. Tissue levels of beta-glucuronidase were very low. This disorder is similar to Sly syndrome in people. The biochemical and molecular defect in affected colony dogs have now been characterized [233,234] and a diagnostic screening test is available for detecting clinically normal carriers [235]. Bone marrow transplantation results in some improvement in the cardiovascular abnormalities in canine mucopolysaccharidosis VII [236], while gene transfer of low levels of beta-glucuronidase corrects hepatic lysosomal storage [237]. Recent studies indicate that neonatal gene therapy can prevent the clinical manifestations of MPS VII in dogs [268].

MPS VII has also been reported in a 12 to 14 week old male Domestic Shorthair cat with signs of walking difficulties (most of the weight was shifted to the front legs) and an enlarged abdomen. Facial dysmorphism, plump paws, corneal clouding, small ears, granulation of neutrophils, vacuolated lymphocytes, and a positive urine test for sulfated glycosaminoglycans suggested mucopolysaccharidosis. Activity of beta-glucuronidase was absent in leukocytes and markedly reduced in fibroblasts, thus establishing the diagnosis of mucopolysaccharidosis VII. Light microscopic examination revealed foam cells in virtually all organs examined, and electron microscopic examination showed pancytic storage of floccular material characteristic of mucopolysaccharides. Stored sphingolipids in the form of zebra bodies were seen in ganglion cells of the CNS and in smooth muscle cells of blood vessels. The molecular basis of feline beta-glucuronidase deficiency has been determined and a screening test is available for detecting clinically normal carriers in a breeding colony [238].

### **Sphingomyelinosis (Niemann-Pick Disease)**

Sphingomyelinosis or sphingomyelin lipidosis denotes a heterogeneous group of lysosomal storage disorders marked by prominent organomegaly. In people, this condition is known as Niemann-Pick disease, and recent publications suggest there are several types (types A, B, C, D, and E) all of which have neurological involvement except types B and E [199]. Approximately 50% of the affected human patients with severe neurological signs belong in the type A group. Type C disease produces moderate neurological signs. The enzyme defect in types A, B, and C is sphingomyelinase; no defect has been identified as yet in type D disease, and the storage product in all types is sphingomyelin, a molecule containing a ceramide, a phosphoric acid ester, and choline [199]. Sphingomyelinase catalyses the hydrolysis of sphingomyelin to ceramide and phosphorylcholine.

In small animals, sphingomyelinosis has been reported in a 5 month old Miniature Poodle dog [239], a 5 month old Domestic Shorthair cat [240], in 3 to 4 month old Siamese cats [241], and in a 7 month old Balinese cat [242]. In the Siamese cats, the condition is inherited as an autosomal recessive trait. The disease results from a profound deficiency of lysosomal sphingomyelinase activity and is thought to be similar to **Niemann-Pick disease type A** [241,243], the most common and most severe form of Niemann-Pick disease that occurs frequently in individuals of Ashkenazi background [244]. Clinical signs in animals include ataxia, hypermetria, continuous head tremors, loss of equilibrium, and splaying of legs. Some animals manifest a stereotypic chewing behavior, lack of appetite and lack of interest in their surroundings. Signs can progress to visual impairment, total paresis and death before animals reach 1 year of age [241]. Hepatosplenomegaly has been seen in affected Siamese cats. In one report in an 11 month old Siamese cat, hepatomegaly but not splenomegaly was observed [245]. Pathological lesions are characterized by widespread cytoplasmic swelling and vacuolation of neurons in CNS and PNS, and foamy macrophages (so-called Niemann-Pick cells) in the bone marrow, lung, spleen, lymph nodes, liver, kidneys, adrenal glands and intestine. Storage material in the foamy cells of non-nervous tissues is reportedly different from those in affected cells of nervous tissues [246] where changes are most marked in Purkinje cells of the cerebellum, neurons of the cerebellar roof nuclei and hippocampus, and in dorsal roots and peripheral ganglion cells. In the spinal cord, affected neurons are especially numerous in the region of the ventral horns [240]. The neuronal changes are associated with nuclear margination and displacement of Nissl substance. Spheroids are commonly seen throughout the brain. Myelination of the brain and spinal cord is normal [242]. Ultrastructurally, neurons contain numerous membranous cytoplasmic bodies and occasional zebra-like bodies, while membranous and vacuolar profiles are reportedly more common in glial cells [242]. Membranous whorls are present in CNS endothelial cells and pericytes. Axonal spheroids contain membrane-bound dense bodies, mitochondria and variable membranous profiles. Many neurons in cerebral cortex, basal ganglia, amygdala, thalamus, and cerebellum show aberrant neurite growth and meganeurite formation, which may indicate dysfunction in the production and regulation of neuronal surface membranes [247]. Most lymphocytes and monocytes in blood smears contain cytoplasmic vacuoles.

A total deficiency of lysosomal (pH 5.0) sphingomyelinase is found in leukocytes, liver, and brain of the cats, although the activity of the microsomal (pH 7.4, magnesium-dependent) sphingomyelinase is normal in brain [241,243]. Cat brains contain an excess of GM2- and GM3-gangliosides, and a nine- to ten-fold excess of sphingomyelin and cholesterol occurs in liver of affected cats. Leukocyte sphingomyelinase levels are about half of the normal level in phenotypically normal littermates of affected kittens suggesting an autosomal recessive mode of inheritance [241].

**Phenotypic Variant of Niemann-Pick Disease Type A** - Characterized by a neuropathic syndrome, with mild or no CNS signs, has been observed in several related and unrelated Siamese cats [248]. Signs in affected animals include absent conscious proprioception, severely depressed to absent spinal reflexes, hypotonia, fine generalized muscle tremors (especially in pelvic limbs), a palmigrade-plantigrade stance, and moderate hepatosplenomegaly. Pain perception and cranial nerve function are normal. Motor nerve conduction velocities are markedly depressed. Positive sharp waves and fibrillation potentials are recorded only sporadically in muscles. While little changes are present in skeletal muscles, peripheral nerves show widespread myelin degeneration associated with many vacuolated macrophages interspersed within the nerve fibers. Remyelination and/or hypomyelination are prominent. Marked vacuolation and granular distension are seen in neurons, glial cells, endothelium, choroid plexus epithelium, and ependyma. Neurons in autonomic and dorsal root ganglia are similarly affected. Vacuolated macrophages, with metachromatic granules, are widely scattered throughout the CNS parenchyma. There is widespread infiltration of virtually every body system with distended granular macrophages. Biochemical analysis of CNS and viscera suggested that the condition in one of these cats was similar to Niemann-Pick disease type A in people [248]. In the other cats, a type A variant was suggested, based on less dramatic increase in sphingomyelin content in liver and kidney, modest increase in brain sphingomyelin content, and lack of detectable enzyme deficiency in known heterozygotes. All cats tested showed severe reduction in CNS and visceral lysosomal sphingomyelinase activity.

**Niemann-Pick Disease Type C** - Another form of sphingomyelinosis has been recognized in Domestic Shorthair cats, similar to the infantile form of Niemann-Pick disease type C (NPC) in people [249-251], an autosomal recessive neurovisceral lysosomal storage disorder in which cholesterol lipidosis results from defective intracellular transport of unesterified cholesterol. A recent study suggests that the underlying defect in the major form of human NPC and this feline model of NPC involve orthologous genes [252]. Affected animals manifest clinical signs around 6 to 9 weeks of age that are similar to those previously described above in cats with Niemann-Pick disease type A: ataxia-dysmetria, whole body tremor, intention tremor of the head, with progression over 4 to 6 months to moving in a crouched gait, loss of menace deficit, inability of cats to right themselves from lateral recumbency, and eventually, generalized disuse muscle atrophy [249]. Other CNS signs seen infrequently in some cats include depressed mentation, vestibular signs, anisocoria and hemiparesis. Affected cats have abdominal enlargement due to palpable hepatomegaly around 8 weeks of age, without clinical manifestations of liver disease [249]. Pathological findings in the CNS included distention and vacuolation of many neuronal cell populations in brain, spinal cord and ganglia, accompanied by extensive neuroaxonal dystrophy (eosinophilic axonal spheroids), especially in the cerebellar folia. Myelin loss and macrophage infiltration in the white matter of the spinal cord, particularly involving the spinocerebellar tracts have been observed in some cats [249]. Many foamy macrophages are found in liver, spleen, lymph nodes and lungs. Ultrastructural studies of affected tissues and organs show heterogeneous membranous inclusions. Immunocytochemical, histochemical, and Golgi studies indicate that gangliosides and unesterified cholesterol are differentially stored in neurons of the cerebral cortex, cerebellum, and hippocampus, as well as in liver [253]. Clinical neurological signs in feline NPC occur in parallel with neuronal structural alterations suggesting that GABAergic neuroaxonal dystrophy is a contributor to brain dysfunction in this disease [254]. In affected NPC cats, lipid analysis reveals excess cholesterol, glucosylceramide, lactosylceramide and phospholipids, including sphingomyelin, in liver [250]. In addition, levels of brain GM2- and GM3-gangliosides are increased. Sphingomyelinase activity in liver is partially deficient or low normal. Cultured skin fibroblasts have partially decreased sphingomyelinase activity and a decreased ability to esterify exogenous cholesterol [250]. Liver lipid analyses of obligate heterozygote cats demonstrates intermediate cholesterol and sphingomyelin concentrations. Furthermore, vacuolated skin fibroblasts, cortical neurons with intracellular inclusions immunoreactive for GM2-ganglioside, and ultrastructural studies with evidence of storage in liver and brain have been reported in heterozygote NPC cats [255].

Prognosis is poor in cats with sphingomyelinosis. Treatment strategies are being investigated in institutions containing colonies of cats with varying forms of sphingomyelinosis, e.g., therapeutic bone marrow transplantation in cats with NPC [249]. Dietary cholesterol restriction does not appear to alter disease progression in NPC-affected kittens [249,269].

A heterogeneous lipid storage disease similar to the human NPC has also been reported in a 9 month old boxer dog with progressive neurological abnormality [256]. Histological examination revealed marked neuronal storage throughout the CNS and histiocytic storage in the reticuloendothelial system. Ultrastructurally, the neuronal storage consisted of accumulation of concentric membranous inclusions and clusters of dense bodies. The biochemically unesterified cholesterol content was high in the liver and spleen. The brain showed increased levels of lactosylceramide and GM2 and GM3 gangliosides [256].

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## Degenerative Disorders of the Central Nervous System (18-Mar-2003)

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The classification of degenerative disorders of the nervous system is difficult and somewhat arbitrary. Many of these conditions are familial or hereditary, breed-related, and involve degeneration of the nervous system within the first few months after birth. Premature degeneration of any component of the CNS, such as neurons, myelin sheaths or axons, can be considered under the broad panoply of abiotrophies which are disorders associated with an inherent lack of vital trophic or nutritive factor(s) [1]. Other degenerative conditions are yet to be classified and remain in the idiopathic grouping. Nevertheless, it is my intent to discuss the degenerative conditions and not necessarily fit them into tight classification schemes, which can vary from year to year, especially as new information becomes available. Despite this caveat, I have tended to follow a classification scheme used by Summers and colleagues in their veterinary neuropathology text [2], which includes leukodystrophies, hypomyelination, spongy degenerations, neuronal abiotrophies, motor neuron diseases, and several idiopathic degenerative disorders, including Lafora's disease, a degenerative condition usually seen in young adult dogs. Leukodystrophies may be viewed among the group of degenerative, abiotrophic disorders affecting dogs and cats [1]. These conditions are considered to be disorders of myelin synthesis and maintenance and involve CNS myelin with a typically bilaterally symmetrical, often regional, distribution [3]. While axonal necrosis and primary demyelination may be seen, lymphoplasmacytic inflammation is usually not a feature. In people, leukodystrophies are genetic diseases and are thought to represent an inborn error of metabolism due to a defective gene that produces an enzymatic abnormality and metabolic derangement that affects myelin [4]. Abnormalities of central myelinogenesis also occur with hypomyelinating disorders and spongy degenerations. Neuronal abiotrophies are disorders characterized by early or premature neuronal degeneration and death [1]. These disorders most commonly target cerebellar Purkinje cells but can also involve neurons more diffusely. Motor neuron diseases in dogs and cats are further examples of abiotrophic processes, are usually familial or hereditary affecting animals early in life, and typically involve the lower motor neuron, and as such, present with signs associated with a neuropathic syndrome.

The degenerative disorders reviewed in this chapter are presented in alphabetical order, based on the commonly used English names and terminology. The disorders are listed in the table below in relation to their classification within the categories of leukodystrophy, hypomyelination, spongy degeneration of the central nervous system, neuronal abiotrophy, motor neuron diseases, and idiopathic degenerative disorders. This listing also provides direct hyper-links to the sections for each individual disorder within the chapter. Commonly used abbreviations include the following: CT, computerized tomography; EMG, electromyogram; NCV, nerve conduction velocity test; PNS, peripheral nervous system.



**Leukodystrophies**

Dalmatian Leukodystrophy  
 Fibrinoid Leukodystrophy  
 Afghan Hound Myelopathy  
 Miniature Poodle Demyelination  
 Rottweiler  
 Leukoencephalomyelopathy

**Hypomyelination**

Chows  
 Lurcher Hounds  
 Springer Spaniels  
 Samoyeds  
 Weimaraners  
 Bernese Mountain Dogs  
 Dalmatians  
 Cats  
 Miscellaneous

**Spongy Degeneration of the CNS**

Spongy Degeneration in White Matter  
 - Labrador Retrievers  
 - Shetland Sheepdogs  
 - Samoyeds  
 - Silky Terriers  
 - Egyptian Mau Kittens  
 Spongy Degeneration in Gray Matter  
 - Bull Mastiffs  
 - Salukis  
 - Cocker Spaniels  
 - Malinois Shepherd Crosses  
 - Rottweilers  
 - Birman Kittens

**Neuronal Abiotrophy**

Cerebellar Cortical Abiotrophies  
 - Neonatal Cerebellar Cortical Abiotrophy  
 - Kerry Blue Terriers  
 - Gordon Setters  
 - Rough Coated Collies  
 - Border Collies  
 - Australian Kelpies  
 - Labrador Retrievers  
 - Rhodesian Ridgebacks  
 - Coton de Tuléar Dogs  
 - Beagles  
 - Miniature Poodles  
 - Brittany Spaniels  
 - Schnauzer-Beagle  
 - Portuguese Podencos  
 - Old English Sheepdogs  
 - Bernese Mountain Dogs  
 - American Staffordshire Terriers  
 - English Bulldogs  
 - Other Canine Breeds  
 - Cats  
 Multisystem Neuronal Abiotrophies  
 - Swedish Lapland Dogs  
 - Cocker Spaniels  
 - Cairn Terriers  
 - Miniature Poodles

**Motor Neuron Diseases**

Giant-Breed Crosses  
 Swedish Lapland Dogs  
 English Pointers  
 German Shepherds  
 Doberman Pinchers  
 Griffon Briquet Vendéens  
 Salukis  
 Other Canine Breeds

**Motor Neuron Diseases with Neurofibrillary Accumulation**

Brittany Spaniels  
 Rottweilers  
 Collie  
 Cats

**Idiopathic Degenerative Disorders**

Alaskan Husky Encephalopathy  
 Yorkshire Terrier Encephalopathy  
 Central Axonopathy in Scottish Terriers  
 Degenerative Myelopathy  
 Encephalomyelopathy in Young Cats  
 Encephalomyelopathy and Organic Acidopathies  
 Hereditary Ataxia  
 Hereditary  
 Polioencephalomyelopathy of the Australian Cattle Dog  
 Hound Ataxia  
 Idiopathic Vascular Calcification  
 Kooiker Dog Myelopathy  
 Labrador Retriever Axonopathy  
 Lafora's Disease  
 Mitochondrial Encephalomyelopathy  
 Nervous System Degeneration in Ibizan Hounds  
 Neuroaxonal Dystrophy  
 - Rottweilers  
 - Collie Sheep Dogs  
 - Chihuahuas  
 - Papillons  
 - Jack Russell Terrier  
 - Cats

**Afghan Hound Myelopathy**

This neurodegenerative disease (also called Afghan Hound hereditary myelopathy) occurs in Afghan Hounds, of either sex, and has an autosomal recessive mode of inheritance [5-9]. Clinical signs have been noted in dogs between 3 and 13 months of age. Pelvic limb paresis and ataxia often are the first signs observed and affected animals may have a synchronous (bunny hopping) pelvic limb gait. Within 1 to 3 weeks, these signs progress to paraplegia, thoracic limb paresis and/or tetraplegia. Spinal reflexes are usually intact or increased but may be depressed as a consequence of gray matter lesions, and breathing may be abdominal. Urinary incontinence is often seen especially in dogs with decreased pelvic limb sensation [6]. Fecal incontinence may also be present in paraplegic dogs [8]. Death frequently results from respiratory failure. Pelvic limbs and caudal thorax may be analgesic. CSF examination may reveal slight elevations in protein level (40 to 80 mg/dl) without increase in cell count [6]. Blood chemistry values, routine spinal radiography and myelography are usually normal. Grossly, grayish softenings of the white matter may be seen in formalin fixed tissue [8]. Histological lesions are limited to the CNS where they tend to be bilaterally symmetrical. Macro- and microcavitation and necrosis occur in white matter extending from mid-cervical to mid-lumbar segments and are especially severe in mid-thoracic cord segments where all funiculi are affected. Dorsal and lateral funicular damage tapers off in the caudal thoracic region, while ventral funicular lesions continue along the ventral median fissure to mid- or caudal lumbar segments. Rostrally, the dorsal and/or ventral funicular lesions extend to caudal or mid-cervical levels [5]. The fasciculus proprius is usually intact [5,6]. Myelin breakdown is characterized by swelling and fragmentation of myelin sheaths and macrophage infiltration, giving the white matter a vacuolar appearance. The largest cavities tend to occur in the dorsal funiculus and usually contain lipid-laden macrophages and proliferating vessels. Funicular axons remain intact. Gray matter involvement, when present, is confined to the dorsal nucleus of the trapezoid body and to the periphery of the spinal ventral gray columns. In the former, lesions are characterized by spongiform degeneration of the white matter, neovascularization, and hypertrophic astrocytes [5,6]. In areas of gray matter adjacent to affected white matter, variable increase in glial cells and mild central chromatolysis of neurons has been noted [8]. In one report, small foci of malacia were observed in the caudal brainstem and medial olivary nucleus [8]. Ultrastructurally, splitting of the myelin sheath occurs at the intraperiod line. Axonal spheroids are sometimes seen with pleomorphic membranous

bodies and variable whorled neurofilaments.

The cause of these lesions has not been determined. Urine methyl malonic acid is negative and serum vitamin B12 levels are normal [6]. The disorder has been termed myelomalacia [7,8] and necrotizing myelopathy [6]. I have chosen to follow the lead of Summers and colleagues [10] in calling this condition a leukodystrophy because of the apparent preservation of axons, since malacia and necrotizing myelopathy connote destruction of all neuroectodermal elements [5]. This leukodystrophy has some clinical and pathological similarities to the degenerative myelopathy in Kooiker dogs [11]. Prognosis is poor to grave. There is no treatment.

### **Alaskan Husky Encephalopathy**

An episodic, incapacitating and ultimately fatal familial neurodegenerative disorder has been described in Alaskan Husky dogs [12,234]. Four dogs showed neurological signs before the age of 1 year (7 - 11 months) and one animal presented at 2.5 years old. Clinical signs in all dogs were acute in onset and included ataxia, seizures, behavioral abnormalities (including obtundation and propulsive pacing), blindness, facial hypalgesia and difficulties in prehension of food. In surviving dogs, the disease was static but with frequent recurrences of gait abnormalities and seizures. Pathological findings were limited to the CNS and bilateral and symmetrical soft gray cavitated foci were seen grossly in the thalamus and sometimes extended into the caudal brainstem. Microscopic lesions were characterized by neuronal loss, spongiosis, vascular hypertrophy and hyperplasia, gliosis, cavitation and mixed inflammatory infiltration. These lesions were seen as foci of bilateral and symmetrical degeneration in the basal nuclei (caudate nucleus, putamen, and claustrum), midbrain, pons and medulla, in addition to multifocal lesions at the base of sulci in the cerebral cortex and in the gray matter of cerebellar folia in the ventral vermis. The cerebellar changes varied from partial to widespread granule cell depletion and loss of Purkinje cells, but with isolated surviving Golgi neurons in the gliotic granule cell layer. Reactive gemistocytic astrocytes with prominent cytoplasmic vacuolation were observed in the thalamus. Spinal cord lesions were restricted to white matter and were characterized by Wallerian degeneration. In 2 dogs, the lesions were severe, bilaterally symmetrical, and involved the deep areas of the dorsolateral funiculus (corresponding to descending upper motor neurons running within the reticulorubrospinal tract) and the ventral funiculus flanking the ventral sulcus. These changes were most severe in the cervical cord. The nature and distribution of lesions were considered to resemble Leigh's disease (subacute necrotizing encephalomyelopathy) of man, in which several enzyme complexes involved in mitochondrial respiratory metabolism show defects, singly or in combination [13]. Neuronal sparing and astrocytic vacuolation suggested possible astrocytic dysfunction. Initial pedigree studies and test mating suggest an autosomal recessively inherited metabolic derangement of unknown nature as the cause of this breed-specific disorder.

### **Yorkshire Terrier Encephalopathy**

A severe subacute/chronic necrotizing encephalomyelopathy has been reported in young Yorkshire Terriers (onset of signs was between 4 months and 1 year of age) with signs and pathology (Fig. 1, Fig. 2, Fig. 3, Fig. 4 and Fig. 5) similar to those found in the above-mentioned encephalopathy of the Alaskan Huskies [221,238,240].



Figure 1. Bilaterally symmetrical thalamic cavitation (\*). Woelcke-Schroeder stain. Courtesy, Dr. Kaspar Matiasek, University of Munich. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 2. Intact nerve fiber (arrowhead) within cavitation. Bodian stain. Courtesy, Dr. Kaspar Matiasek, University of Munich. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

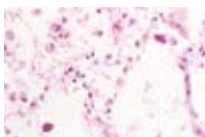


Figure 3. Gitter cells and intact neurons within cystic lesions. Hematoxylin & eosin (HE). Courtesy, Dr. Kaspar Matiasek, University of Munich. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 4. Spongy change and vascular proliferation, cerebral cortex. HE. Courtesy, Dr. Kaspar Matiasek, University of Munich. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 5. Severe depletion of Purkinje cells and granule cells, along with proliferation of Bergmann glia. HE. Courtesy, Dr. Kaspar Matiasek, University of Munich. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

CSF findings may include elevated protein concentration and a mononuclear pleocytosis. Multifocal, extensive areas of decreased opacity throughout the cerebral hemispheres, asymmetric ventriculomegaly, and lack of contrast enhancement were found on CT images of 3 affected dogs with multiple malacic cavitations within the brain [238]. In this report, the condition was termed a "necrotizing meningoencephalitis" which needs to be differentiated from the multifocal non-suppurative necrotizing encephalitis reported in Yorkshire Terriers in Switzerland [239], in which no malacic cavitations were described.

### Central Axonopathy in Scottish Terriers

A central axonopathy in 2 male and 1 female Scottish Terrier puppies from 3 different but related litters (sharing a common sire) has been reported [189]. Clinical signs consisting of severe whole-body tremors and ataxia were first detected at the age of 10 to 12 weeks. They worsened with activity and excitement and diminished during rest or sleep. Two dogs also had paraparesis. In one dog the neurological deficits progressed over several months. No abnormalities were seen on gross examination. Neuropathological examination revealed widespread axonal changes, vacuolation, and gliosis in the white matter of the CNS. Diffuse thickening or increased diameter was seen in many axons in the lateral and ventromedial funiculi and to a lesser extent in other white matter areas. Some axons appeared quite large, but with little fragmentation or dystrophic swellings. Myelin sheaths were thin or absent around these fibers. Myelin stains revealed decreasing staining intensity in the spinal cord. Similar, but less intense changes were present throughout white matter of the brainstem, cerebellum, and cerebrum. Status spongiosis and gliosis were seen in the white matter of the brain, brainstem, and spinal cord, and in gray matter of some nuclei of the brainstem, thalamus, and cerebellum. Occasional dystrophic axons were seen in nuclear areas of the brainstem and thalamus, in the granular layer of the cerebellum, and in the internal capsule, suggesting that the thickened axons might eventually progress to degeneration. Peripheral nerves were normal. The authors suggested that this may be an inherited condition with a poor prognosis, based on the progressive clinical course in one puppy.

### Cerebellar Cortical Abiotrophies

Cerebellar cortical abiotrophies are characterized by premature aging, with degeneration and death of various neuronal cell populations, and are the most common neuronal abiotrophies in small animals [1]. Clinical signs of cerebellar syndrome (e.g., ataxia-dysmetria, head tremor, broad-based stance, and loss of balance) occur most commonly in young animals that are clinically normal at birth, usually within a few weeks or months after birth. This "juvenile" onset encompasses most cases of cerebellar abiotrophy, although in some instances, there is an adult onset. Occasionally, a neonatal cerebellar abiotrophy is seen in which animals show cerebellar signs at birth (see below). The clinical course is typically progressive.

Antemortem diagnosis is suggested by clinical signs, age, breed, and by rule-out of acquired diseases. Examination of biopsy material from selected sites such as the cerebellum may confirm an antemortem diagnosis in some instances. Some cerebellar disorders are limited to Purkinje cells and to the anatomically- and developmentally-related granule cell layer. Reduction in numbers of granule cells might reflect degeneration or loss of Purkinje cells. Occasionally, retrograde degeneration occurs in other neuronal populations that project to the cerebellar cortex, such as olivary neurons that project to Purkinje neurons, and pontine neurons that project to granule cell neurons [1]. Regressive changes in neurons of cerebellar nuclei are regarded as transsynaptic degeneration following the Purkinje cell damage [14]. More recent reports indicate that some cerebellar disorders are accompanied by cerebral cortical neuronal degeneration (see multisystem neuronal abiotrophy in Miniature Poodles). In general, electrodiagnostic studies, serum biochemistry, and CSF analysis are of limited value in the diagnosis of degenerative cerebellar disorders, although imaging techniques might demonstrate cerebellar atrophy. Prognosis is guarded to poor. Presently, there is no treatment.

Cerebellar cortical abiotrophies have been reported in several breeds of dogs, as well as in cats, and each condition is discussed separately.

**Neonatal cerebellar cortical abiotrophy** has been identified in beagles [14,65] (see below), Samoyeds [65], and in Irish Setter puppies with hereditary quadriplegia and amblyopia (HQA), a condition associated with a fully penetrant, autosomal recessive gene [69]. Microscopic lesions included diffuse loss of Purkinje cells and variable loss of granule cells in the Beagles and Irish Setters, and swollen axons of Purkinje cells along with occasional myelin degeneration and axonal necrosis in the folia white matter of Beagles, Irish Setters, and Samoyeds [65,69]. Interestingly, microscopic lesions were not detected in the Irish Setters until around 3 months of age. A similar condition has been reported in Coton de Tuléar and Rhodesian Ridgeback puppies (see below).

#### **Cerebellar Cortical Abiotrophy in Kerry Blue Terriers**

This is an autosomal recessive disease that affects Kerry Blue Terriers [15]. Clinical signs of pelvic limb stiffness and head tremors reflect cerebellar disease and are seen between 9 and 16 weeks of age. Subsequent signs include dysmetria-hypermetria and often, an inability to stand by 1 year of age. The CNS lesions are progressive and tend to follow a relatively well-defined temporal course [16]. Degeneration of Purkinje cells in the cerebellar cortex is evident at the onset of clinical signs (approximately 2 to 4 months of age). After two weeks to one month of clinical illness, retrograde transsynaptic neuronal degeneration occurs in the olivary nucleus. Degeneration of both large and small neurons in the caudate nucleus begins approximately two to three months after the onset of clinical signs, and by seven to eight months of clinical illness, the caudate nucleus is reduced to numerous microcystic cavities and is almost devoid of neurons except for a narrow subependymal zone and the tail of the nucleus. Neuronal depletion in the pars reticularis of the substantia nigra, evident after five to seven months of clinical illness, is attributed to an anterograde transsynaptic mechanism of neuronal degeneration. Ultrastructural changes have been reported [17]. In the caudate nucleus, the initial lesion was mitochondrial hypertrophy in dendrites of intrinsic neurons. Degeneration of these neurons became widespread while axons of passage and terminal boutons were spared. During the final stages, there was severe disruption of the neuropil with loss of both neurons and glia. In the cerebellar cortex, the lesions involved principally Purkinje cells and progressed through a pattern of degeneration comparable to that involving intrinsic neurons of the caudate nucleus, with eventual astroglial scarring of the molecular layer. In contrast to the caudate nucleus, there was no disruption of the neuropil with loss of structure in the cerebellum. A disorder of glutamate metabolism with associated excitotoxic injury to Purkinje cells and neurons of the caudate nucleus has been proposed [16,17]. The condition is progressive and prognosis is poor.

#### **Cerebellar Cortical Abiotrophy in Gordon Setters**

This is believed to be an autosomal recessive, late-onset cerebellar disease affecting mature Gordon Setters between 6 and 30 months of age [18,19]. Dogs appear normal during the first 6 months of life, but between 9 and 18 months, they develop a mild thoracic limb stiffness, hypermetria, broad-based stance, and occasional stumbling. Nystagmus can occur late in the condition. These signs progress very slowly (e.g., over several years) or remain static after a short period of progression. Lesions are restricted to the cerebellum. There may be gross atrophy of the cerebellar cortex, particularly the pars intermedia. Microscopic changes are characterized by profound loss of Purkinje cells throughout most of the cerebellar cortex, although the vermis and paravermian regions of lobules IV, V, and VI were especially affected in one report [20]. The molecular layer is moderately thinned and the granule cell layer varies in thickness. Ultrastructural findings include a reduction in the size of Purkinje cells, axonal degeneration, and synaptic abnormalities in the cerebellar glomeruli and deep nuclei of the cerebellum, suggesting that the degenerative process begins in Purkinje cells and that granule cells may be secondarily affected [21]. Prognosis is guarded.

#### **Cerebellar Cortical Abiotrophy in Rough Coated Collies**

This is an autosomal recessive disease reported in Rough Coated Collie dogs in Australia [22]. Posterior incoordination occurs between 1 and 2 months of age. Subsequently, animals develop a broad based stance, hypermetria and head tremors and occasionally, a bunny-hopping gait. Affected animals frequently fall sideways or forwards with their legs in extension. Severely affected dogs typically spend most of their time lying down. Clinical signs may stabilize after 12 months of age. Pathologically, there is early and rapid degeneration of Purkinje cells and granule cells of the cerebellum. Other changes include neuron depletion in cerebellar roof nuclei, lateral vestibular nuclei, inferior olivary nuclei, and ventral horns of spinal cord. Additionally, Wallerian degeneration may be observed in the brainstem and in lateral and ventral funiculi of the spinal cord.

#### **Cerebellar Cortical Abiotrophy in Border Collies**

This condition appears to be very similar to that described in the Rough Coated Collie [23]. Clinical signs are first noted at 6 to 8 weeks of age and are characterized by ataxia, hypermetria and head tremor. There is loss of granule and Purkinje cells from the anterior folia of the cerebellar vermis, which is flattened grossly. The disease is believed to be familial. Prognosis is guarded to poor since clinical signs reportedly deteriorate with time. An unusual form of abiotrophy has been reported in two

sibling Border Collies in which there was extensive loss of the cerebellar granular cell layer with relative sparing of Purkinje cells [229].

#### **Cerebellar Cortical Abiotrophy in Australian Kelpies**

This degenerative canine condition is thought to be genetically transmitted as an autosomal recessive trait [24]. Clinical signs usually begin around 6 weeks of age, but may be delayed until 12 weeks of age, and are characterized by ataxia, hypermetria, head tremor, truncal ataxia, and proprioceptive deficits. Menace response may be absent. There is regional loss of Purkinje cells and granule cells and mild spongiosis and Wallerian degeneration in white matter tracts of affected cerebellar folia. Changes are most severe in lingula, central and culmen lobules of the cerebellar vermis. Occasionally, necrotic Purkinje cells are present. White matter spongiform changes may be seen in cerebellar dentate nuclei and in vestibular nuclei. Prognosis is poor.

#### **Cerebellar Cortical Abiotrophy in Labrador Retrievers**

This degenerative condition has been described in three Labrador Retriever puppies from a litter of twelve [25]. Clinical signs occur about 12 weeks of age and include pelvic limb ataxia, hypermetria, truncal ataxia, and wide-based stance. Within a week, signs progress rapidly to thoracic limb involvement, falling, and inability to walk without assistance. Positional nystagmus and reduced menace response may be noted. Results of laboratory diagnostic testing for toxoplasmosis, canine distemper virus, *Cryptococcus* capsular antigen, and electroencephalography were normal. The genetic status of this condition remains to be confirmed. Grossly, the cerebellum is smaller than normal. There is loss of Purkinje cells and granule cells, granule layer thinning, and folia white matter gliosis in all regions of the cerebellar cortices, especially in central and lingula lobules of the rostral vermis. The culmen and declive lobules are affected later in the disease. Retrograde degeneration of brainstem nuclei is not observed.

A similar disorder has been seen in a puppy of predominantly Labrador Retriever breeding (the mother was a purebred Labrador Retriever and the father was a Labrador-Chesapeake Retriever cross) [26]. The clinical signs were similar to those described above; however, the progression was very slow and the dog required no assistance to walk, even at one year of age. Also, abnormal nystagmus was not seen. This dog exhibited seizure-like episodes similar to those described for Gordon Setters (see above), characterized by progressing episodes of recumbency with opisthotonus and muscle rigidity. Gross and microscopic findings were similar to those seen in the Gordon Setters, although neuronal loss and/or axonal swelling was found in the olivary and vestibular nuclei, along with swollen axons in the vestibular nerve in the region of the cochlear nucleus. Axonal spheroids were seen in the cerebellar nuclei. These changes were considered to represent transynaptic degeneration as a consequence of Purkinje cell loss. Increased numbers of Bergmann's astrocytes were seen around Purkinje cells and there were increased numbers of astrocytes in the cerebellar white matter.

#### **Cerebellar Cortical Abiotrophy in Rhodesian Ridgebacks**

An unusual syndrome of cerebellar Purkinje's cell degeneration and coat color dilution has been reported in a family of Rhodesian Ridgeback dogs [27]. Three puppies were presented for growth retardation, inability to ambulate, and progressive ataxia. Signs were usually seen by 2 weeks of age. By 4 weeks, ataxia was so severe that affected pups were unable to stand or maintain a sternal posture, and tended to lie on their sides making spasmodic limb movements when stimulated. At this time, affected puppies were one-half the size of their normal littermates. They often assumed an opisthotonic posture with rigid extension of forelimbs, and the hind limbs were flexed at the hip, bringing these limbs forward under the body. Intention tremor of the head was noted, especially during eating and playing. Horizontal nystagmus was also observed, particularly after stimulation of the retina with a light beam. All affected pups and none of the normal littermates had a dilute coat color at birth. The iris of affected pups was blue rather than the dark brown to light amber color normally seen in this breed. Results of routine laboratory tests, urine metabolic screenings, and karyotype analyses were normal. Grossly, the cerebellum was smaller than normal, including the vermis and hemispheres. Microscopic changes were limited to the cerebellum. Folia were small, with thinning of the granular and molecular layers, and there was marked reduction in Purkinje cell numbers (note that the microscopic changes were not detected until around 1 month of age). Occasional necrotic Purkinje cells had nuclear pyknosis and cytoplasmic eosinophilia. These changes were most prominent in the dorsal vermis and flocculus. Swollen, eosinophilic Purkinje cell dendrites were present in the molecular layer, associated with Purkinje cell necrosis and depletion. There were increased numbers of astrocytes with large nuclei throughout the molecular layer. The granule cell layer was hypocellular, particularly in areas of Purkinje cell loss. Histological examination of a skin sample revealed uneven distribution of macromelanosomes within hair shafts. Pedigree analysis suggested an autosomal recessive mode of inheritance. This is the first description of a genetic syndrome affecting the CNS and associated with coat color dilution in dogs. While the molecular basis for this condition is unknown at this time, present evidence supports the hypothesis of a single gene mutation with pleiotropic effects [27].

### **Cerebellar Cortical Abiotrophy in Coton de Tuléar Dogs**

A neonatal ataxia syndrome has been described in Coton de Tuléar puppies [225] with signs very similar to those seen in the Rhodesian Ridgeback puppies, with most of the affected pups being unable to stand and having a propulsive "swimming" form of gait. They frequently would fall to lateral recumbency with subsequent decerebellate posturing and paddling. Ocular motor abnormalities included fine vertical tremors at rest and saccadic dysmetria. The condition was nonprogressive at least until 4 months of age. No specific abnormalities were identified in blood, urine, CSF cellularity/protein (although a mild increase in protein concentration was observed in one dog), CSF organic and amino acid concentrations, brain imaging (MRI/CT), and electrodiagnostic testing (brain stem auditory-evoked potentials, EMG, nerve conduction studies). Microscopic lesions were not seen in the CNS or muscle/nerves using light microscopy or immunocytochemical techniques, although ultrastructural studies of the cerebellum showed synaptic abnormalities, including loss of presynaptic terminals and organelles associated with parallel fiber varicosities within the molecular layer and increased numbers of lamellar bodies in Purkinje cells. An autosomal recessive trait affecting development of the cerebellum is suspected. Remarkably, an unusual form of cerebellar granuloprival degeneration has also been in three male Coton de Tuléar puppies between 12 and 14 weeks of age showing progressive cerebellar signs beginning at 8 weeks after birth. Signs included generalized ataxia with hypermetria, tendency to fall, intention tremor and abnormal menace response. Grossly, the cerebellum appeared shrunken. Histopathologically the granular cells were diminished or almost completely absent. However, with the exception of some swollen Purkinje cell axons ("torpedos") in the granular layer, Purkinje cells did not appear to be reduced in number and did not show degenerative changes. There was a marked gliosis in the molecular layer, and occasionally small inflammatory foci were present in the cerebellar cortex. A marked diffuse T cell infiltration (CD3(+) cells) occurred in the lesions (B cells were not seen). CD18 staining showed an upregulation of microglial cells at the lesion site. The lesions resembled some forms of paraneoplastic syndromes in people believed to be caused by an autoimmune mediated T cell reaction [227]. The authors state that this congenital condition in the Coton de Tuléar dog breed could be based on a genetically defined immune defect leading to autoimmune destruction of the granular cells.

### **Cerebellar Cortical Abiotrophy in Beagles**

A degenerative cerebellar disease has been reported in Japan involving three Beagle puppies from a litter of eight [14]. Clinical signs began at 3 weeks of age and were characterized by frequent falling. Signs were progressive. The cerebellum appeared smaller than normal. Lesions were confined to the cerebellum and were characterized by thin folia and widened sulci, extensive degeneration and loss of Purkinje cells, thinning of molecular and granule cell layers, and granule cell depletion. Axonal torpedoes (a non-specific sign of Purkinje cell degeneration) were seen in the granule layer. The cerebellar hemispheres were most severely involved followed by rostral parts of the culmen and declive of the vermis. The genetic status of this condition remains to be confirmed. A similar, early onset disorder reported in a Beagle puppy in the USA was considered to be inherited as an autosomal recessive trait [28].

### **Cerebellar Cortical Abiotrophy in Miniature Poodles**

This degenerative condition is described under multisystem neuronal abiotrophy.

### **Cerebellar Cortical Abiotrophy in Brittany Spaniels**

This late-onset cerebellar disorder has been observed in older, usually spayed, Brittany Spaniels [29,30]. Onset of signs occurs between 7 and 14 years of age. Clinical signs are slowly progressive, sometimes extending over a 4-year course. Subtle limb spasticity and hypermetria eventually leads to truncal ataxia, head tremor, "lurching" gait, "saluting" movements in the thoracic limbs, frequent falling, and inability to stand. Terminally, dogs crawl in a crouched thoracic posture with neck extension. Results of all diagnostic testing, including CSF analysis, are normal. The cerebellum is grossly normal. Microscopic lesions are confined to cerebellum, medulla oblongata and spinal cord. The most severe lesion is diffuse Purkinje cell loss (approximately 20%) throughout the cerebellar lobules, particularly in the vermis, with massive neurofilament accumulation in degenerating cells. Neurofilamentous accumulation in Purkinje cells and their processes appears to precede necrosis. Axonal spheroids are scattered in granular and deep molecular layers. There is some bilateral neuronal degeneration in the dorsal horns of the spinal cord and in the gracilis and cuneate nuclei. There is bilateral sporadic axonal degeneration in the dorsal columns and lateral and ventromedial areas of the spinal cord. The genetic status of this condition remains to be confirmed.

An unusual cerebellar abiotrophy characterized by granular cell loss has been reported in an intact, male Brittany Spaniel (3 years old), with a history of ataxia and head tremors of more than 6 months duration [31]. Grossly, the cerebellum was symmetrically smaller than normal and represented < 6% of the total brain weight (normal is 10%). Histological examination showed an unusual form of cerebellar abiotrophy characterized by marked and diffuse depletion of the granular and molecular layers of the cerebellum with normal morphology and numbers of Purkinje cells. The marked loss of neurons in the granular layer was thought to be due to an innate metabolic error of granule cells and that concomitant decreased

thickness of the molecular layer might be expected because of the decreased excitatory input from granule cell parallel fibers. It was reasoned that the slight changes in Purkinje cells was expected because the major excitatory input comes from brainstem nuclei, with only minor excitation evoked from granule neuron synapses.

#### **Cerebellar Cortical Abiotrophy in a Schnauzer-Beagle Dog**

Late-onset cerebellar degeneration has been reported in a 6 year old male Schnauzer-Beagle dog with clinical signs similar to those seen in Brittany Spaniels [32]. The condition progressed slowly over a 5-year period to a point where the dog was unable to walk, eat or drink without assistance. Cerebellar biopsy revealed reduction in size of the cerebellar hemispheres and vermis, loss of Purkinje cells and granule cells, Purkinje cell degeneration, and thinning of the molecular layer. Some Purkinje cells were displaced into the granule cell layer.

#### **Cerebellar Cortical Abiotrophy in Portuguese Podencos**

Cerebellar cortical abiotrophy has been reported in two Portuguese Podenco littermates [33]. Clinical signs had an early onset around 2 to 3 weeks of age and were characterized by progressive cerebellar ataxia. Lesions were confined to the cerebellar hemispheres and characterized by extensive loss, degeneration, and necrosis of Purkinje cells. An autosomal recessive pattern of inheritance was suspected.

#### **Cerebellar Cortical Abiotrophy in Old English Sheepdogs**

A slowly progressing, late-onset form of cerebellar degeneration characterized by progressive gait abnormality has been reported in Old English Sheepdogs, with an apparent autosomal recessive mode of inheritance [34]. Clinical signs began when dogs were from 6 to 40 months of age and were characterized by wide-based stance in hind limbs, hypermetric forelimb gait, and inconsistent menace deficit. As the disease progressed, truncal ataxia progressively worsened, often with dragging of the toes, and ambulation became increasingly difficult, with frequent falling and difficulty rising from a recumbent position. Some dogs developed a fine head tremor. The course of the disease developed slowly over many months to several years. The cerebellum appeared grossly normal. Microscopically, there was localized loss of Purkinje cells with gliosis, thinning of the granule cell layer, and increased cellularity of the molecular layer. These changes were restricted to the folia of the paravermal and vermal cerebellar cortex. There was also a marked increase in glial cell numbers in the cerebellar nuclei. Interestingly, 4 of 22 dogs in this study had no histological cerebellar changes but had clinical signs of cerebellar degeneration.

#### **Cerebellar Cortical Abiotrophy in Bernese Mountain Dogs**

An unusual disorder has been reported in Bernese Mountain Dogs characterized by progressive cerebellar and hepatic disease [35]. Clinically, stiffness in the hind limbs, mild incoordination, and a slight head tremor were first noticeable when pups were 4 to 6 weeks old. As the condition progressed, pups assume a wide-based stance. Other signs included head bobbing, spontaneous nystagmus, and, finally, paresis. Hematologic findings included leukocytosis with a left shift; normocytic, normochromic anemia; hypoproteinemia, low serum creatinine, and urea nitrogen concentrations; excessive fasting plasma ammonia concentration; and an increase in concentration of serum bile acids. Portal venography performed on 1 dog revealed a small liver and extensive extrahepatic varicosities. Necropsy revealed cerebellar hypoplasia, nodular liver, extensive abdominal varicosities, and ascites. Histologically, degeneration and depletion of Purkinje's cells and vacuolation, degeneration, and nodular regeneration of hepatic tissues were evident. Preliminary analysis of the pedigree suggested an autosomal recessive pattern of inheritance.

#### **Cerebellar Cortical Abiotrophy in American Staffordshire Terriers**

A disorder has been recently recognized in American Staffordshire Terriers in the United States (Dr. Natasha Olby, personal communication, 2001) and in Europe [217,220] with adult onset, slowly progressive cerebellar signs. Clinical signs develop between 2.5 and 6 years of age and include ataxia, spontaneous nystagmus and falling over. Neurological examination reveals ataxia in all limbs with normal conscious proprioception and, as the signs progress, worsening hypermetria and truncal ataxia. Strength is normal. Dogs ambulate well on flat straight surfaces, but tend to trip, stagger, or fall over as soon as they attempt to turn quickly, negotiate a door, or go down steps. Affected dogs often fall over when they shake their heads. In some instances, dogs assume an opisthotonic posture after falling. Spontaneous nystagmus (horizontal, rotary and vertical) is easily elicited by sudden movements. Menace reaction may be absent in severely affected dogs. To date, CSF analysis, and metabolic screening have been normal. Imaging studies have revealed asymmetrical lateral ventricular dilatation (CT scans) and symmetrical cerebellar atrophy (MRI scans) [220]. Histopathological findings include complete absence of Purkinje cells in cerebellar cortex, increased density of Bergmann glia in the Purkinje layer, and thinning of molecular and granular layers. Pedigree analysis is compatible with an autosomal recessive inheritance.

### **Cerebellar Cortical Abiotrophy in English Bulldogs**

Clinical signs characterized by wide-based stance, generalized intention tremors, hypermetria in all limbs, decreased menace response and slight proprioceptive deficits have been described in 3 young English Bulldogs (between 5 and 8 months of age) born from the same parents [223]. Onset of signs was around 2 months of age. A CT scan on one dog was normal. No gross abnormalities were noted in the CNS. Histopathology was limited to the cerebellum and included severe Purkinje cell loss and marked gliosis in Purkinje and granule cell layers. Occasional Purkinje cells were located in molecular and granule cell layers. The condition is believed to be inherited.

### **Cerebellar Cortical Abiotrophy in Other Canine Breeds**

Cerebellar degenerations, usually involving Purkinje cells, have been reported in families of Samoyeds (with swollen axons of Purkinje neurons in the granule cell layer), Airedale Terriers, Finnish Harriers, and Bern Running Dogs [36]. A genetic basis has been suggested. A similar disorder has been observed in single litters of Akitas, Clumber Spaniels, Golden Retrievers, Cocker Spaniels, Cairn Terriers, Fox Terriers, Great Danes, and mixed-breed dogs [36]. Cerebellar cortical abiotrophy has recently been reported in a Scottish terrier using magnetic resonance imaging [230]. At Auburn University, we have observed isolated cases of Purkinje cell degeneration and loss in German Shepherd, English Springer Spaniel, Miniature Poodle, and Pit Bull Terrier puppies aged between 6 and 16 weeks. Clinical signs are characterized by the typical cerebellar syndrome.

### **Cerebellar Cortical Abiotrophy in Cats**

Cerebellar cortical abiotrophy-degeneration is considered rare in cats [10]; however, late onset cerebellar degeneration was diagnosed in a one-and-a-half year old Siamese cat [37]. The cat presented with mild ataxia involving all four limbs. Over the following two years, the signs gradually progressed to severe incoordination, a frequent tendency to fall, and a head tremor. Profound and diffuse Purkinje cell loss and evidence of brainstem Wallerian degeneration were found on histopathological examination, but no etiological agent was detected. A similar clinical history was noted in a 4 year old male Domestic Shorthair cat with signs of symmetrical hypermetria and spasticity, whole body tremor, intention tremors of the head, positional vertical nystagmus, and loss of balance [191]. In addition, the cat had bilaterally absent menace response and widely dilated pupils with diminished pupillary light response. Fundoscopic exam revealed end-stage retinal degeneration, pale optic disks and retinal vessel attenuation. Grossly, the cerebellum was approximately two-thirds the normal size. Microscopic lesions were restricted to the cerebellum and included marked reduction/loss of Purkinje cells in all folia and 'empty baskets', along with diminished molecular layer and increased numbers of Bergmann's glia. Photoreceptor degeneration was observed in retinal sections associated with pronounced reduction in rod/cone numbers. This case was considered to be analogous to spinocerebellar ataxia type 7 (SCA7) in humans, an autosomal dominant form of cerebellar ataxia with retinal degeneration [192] associated with accumulation of expanded polyglutamine proteins resulting from an expanded CAG (cytosine-adenosine-guanine) sequence [193,194].

There have been recent reports of cats with hereditary cerebellar degeneration, transmitted as an autosomal recessive trait [38,39]. Cats developed cerebellar signs around 7 weeks of age characterized by intention tremor, especially of the head and neck, during eating and drinking, wide-based stance when standing, and ataxia-dysmetria with staggering gait and frequent falling. The clinical course was progressive. The cerebellum was atrophic. Microscopic findings included pronounced loss of Purkinje cells with an increase in Bergmann's glia in the cerebellar hemispheres, preservation of some Purkinje cells in the vermis and moderate neuronal depletion of the olivary nucleus. Cerebellar and pontine nuclei were normal, as were other areas of the brain, spinal cord and peripheral nerves. Electron microscopic examination revealed swelling of the distal dendrites of Purkinje cells in the less-affected nodule of the vermis, and clusters of presynaptic boutons without any synaptic contact in the severely affected folia. Presence of presynapses in the molecular and Purkinje cell layers was confirmed by positive immunoreactivity to anti-synaptophysin. Quantitative ultrastructural analysis revealed an increase in the density and mean size of presynapses in the molecular layer of the severely affected folia. These findings suggested that degeneration of Purkinje cells began at the most distal part of the dendrite, and that presynapses, axon terminals of the granular cells and basket cells may remain for a long time even after complete degeneration of the Purkinje cells [39]. These cats were considered to represent a novel animal model of human spinocerebellar degeneration.

Several other variants of this condition have been reported. An olivopontocerebellar atrophy has been observed in 2 adult feral cats with signs of head and limb dyssynergia and microscopic lesions characterized by loss of cerebellar cortical neurons (Purkinje cells, Golgi and basket cells and granule cells), loss of myelin in vermis and lobules, reduction in pontine nuclei and transverse fibers, and neuronal loss/gliosis in the inferior olivary complex [222]. Cerebellar degeneration involving only Purkinje cells (characterized by cell loss and degeneration including dendritic vacuolization and axonal spheroids) with normal inferior olive and pontine nuclei, has been described from Belgium in two 4 month old female kittens from the same litter with characteristic cerebellar signs [224]. MRI in one kitten was normal. The cerebellum was grossly normal. A similar condition has been reported from the U.K. in two domestic shorthair littermate kittens with signs occurring



around 7 - 8 weeks of age [228]. Cerebellar abiotrophy has also been reported in cats with neuraxonal dystrophy.

### **Dalmatian Leukodystrophy**

A progressive neurological disorder, transmitted by autosomal recessive inheritance, was described in male and female Dalmatian dogs [40]. Clinical signs were noted between 3 and 6 months of age and were characterized by visual deficiency and progressive ataxia, initially in the hind limbs, then involving all limbs, sometimes progressing to the point where the dog could no longer stand. Results of routine hematology, urinalysis, and CSF analysis were within normal limits. Gross pathological findings included brain atrophy, dilatation of lateral ventricles, and cavitation of the central white matter of the cerebral hemispheres, primarily involving the centrum semiovale. The subcortical arcuate fibers (U-fibers) of the cerebral white matter appeared to be spared. The occipital lobes were usually more severely involved than more rostral areas of the brain. Bilaterally symmetrical grayish and somewhat depressed areas, and occasional foci of softening, were also found in the corpus callosum. Microscopic lesions occurred in internal and external capsules, caudate nucleus and claustrum (sometimes with microscopic cavities in these basal ganglia), optic nerve, and less frequently, the spinal cord where lesions were mainly confined to the ventral horns and adjacent white matter in thoracic cord segments. A few cases had vacuoles within the spinal cord white matter adjacent to the gray matter and beneath the meninges. Within affected areas of white matter, there was a diffuse loss of myelin, widespread vacuolation, edema, presence of numerous, lipid-filled macrophages, and reactive astrocytosis. Axons appeared to remain intact, at least initially. Vacuolation was seen in myelin sheaths as a result of lamella splitting. Spinal roots and peripheral nerves were unaffected. Prognosis was poor. There is no treatment. To my knowledge, there have been no additional reports of this disease during the past 15 years; however, very similar clinicopathological findings have been reported in 2 related Labrador Retriever puppies [237].

### **Degenerative Myelopathy**

This degenerative disease may have an inherited basis in dogs [41] and it may represent an abiotrophy [1]. It is most often observed in German Shepherd dogs over 5 years of age; however, a similar clinical and pathological condition has been reported in young German Shepherd dogs [42], other breeds of dogs [43-46], and cats [47]. The onset of the disease is insidious. Initial signs include pelvic limb ataxia and paresis. Ataxia, in the form of hypermetria or excessive circumduction of the limb, crossing of the legs when walking with one limb catching behind the other, is greater than paresis, seen as dragging the toes and flexing the stifles when weight-bearing [45]. The signs progress slowly to truncal ataxia and severe pelvic limb paresis. Knuckling of paws of pelvic limbs is commonly observed, with wearing of the nails of the affected pelvic limb(s). The cutaneous trunci reflex is usually intact. Deep pain perception is unimpaired. Some dogs have a depressed patellar reflex. Sphincter function remains normal. The disease usually is slowly progressive over 6 to 36 months, although fluctuations in clinical signs may be seen [48].

Grossly, spinal ganglia, dorsal and ventral roots and rootlets are normal. Histopathologically, white matter changes are found throughout the length of the spinal cord, with the most severe lesions being present in the thoracic cord. Lesions are characterized by degeneration of white matter, especially in dorsolateral and ventromedial funiculi, along with degenerating dystrophic axons, swollen myelin sheaths, often with macrophages, astrocytosis, and gliosis. Axons may fragment and disappear. The lesions are bilateral but not necessarily symmetrical, are not restricted to particular fiber tracts, and on longitudinal studies, appear not to be continuous [41]. Lesions typically do not extend into the brainstem [46]. However, at variance with all previous reports, a recent study documented chromatolysis, gliosis and neuronal loss in various brain neurons, including the red nucleus, lateral vestibular nucleus and, occasionally, in the dentate nucleus [49]. The significance of these changes is uncertain, especially since the authors found similar lesions in dogs with spinal injuries. Leptomeningeal thickening and fibrosis has been noted [46]. Dorsal root involvement and loss of neurons in dorsal gray horns (Clarke's column) of spinal cord have been observed in some German Shepherds [45,46], although this may be an age-related effect [50]. Ventral roots are unaffected. Occasional dorsal root ganglion cells show minor central chromatolysis [45]. No significant changes are seen in brain, peripheral nerves or muscles, including end-plates and spindles [41,45,46].

The pathogenesis of this disease is unknown. It is unrelated to intervertebral disk degeneration, spondylosis deformans or osseous metaplasia of dura mater. Trauma and vascular disease have been suggested as possible causes [46], but have not been substantiated. Some affected dogs have an associated enteropathy characterized by biochemical changes in peroral jejunal biopsies and accompanied by overgrowth of bacteria in duodenal juice, and decreased serum levels of tocopherol (vitamin E) and cobalamin (vitamin B12) [51-53]. The significance of these findings remains unclear and a recent study refutes vitamin E involvement [49] (See vitamin E deficiency, in Nutritional Disorders). The clinical course of the disease in dogs with low levels of vitamin B12 has not been reversed by parenteral administration of cobalamin [52]. Morphologic and morphometric data [41] do not support the hypothesis that this disease represents a "dying back" neuropathy [45]; although this theory involving distal involvement of motor and sensory fibers is still favored by some [49]. Another theory is that degenerative myelopathy is an immune-mediated neurodegenerative disease [54]. Depression of cell-mediated immune responses (to concanavalin A, phytohemagglutinin P and pokeweed mitogens reportedly occurs secondary to a progressive

increase in the number of circulating suppressor cells [55,56]. Affected dogs have 3 to 10 times more circulating immune complexes than normal dogs, including a possible protein-specific antigen with a molecular weight of 85 kD, and plasma cell infiltrates are reportedly found in several organs, including kidneys and intestinal tracts [48]. Furthermore, an immunohistochemical study on German Shepherd dogs with degenerative myelopathy reports focal staining for immunoglobulin G (IgG) and the third component of complement (C3) in spinal nerve tracts characteristically affected in degenerative myelopathy [57]. Deposition of IgG and C3 is also found with large and small blood vessels and in other areas independent of visible lesions, suggesting that IgG and C3 deposition may precede histological evidence of spinal cord damage. Degenerative myelopathy may well be a genetic, late-onset neurodegenerative disease [45,49]. Griffiths and co-workers are searching for candidate genes [49]. A study aimed at characterizing the histopathology, antemortem diagnostics (myelography/MRI and electrophysiology), excitotoxicity/oxidative stress in CSF (glutamate, methionine, prostanooids) and genetic factors is currently being undertaken at Texas A and M University with Dr. Joan Coates as the senior investigator. Diagnosis is based on clinical syndrome, breed, and age. Hematology, blood chemistries, urinalysis, and CSF analysis are normal (although an elevation in protein in CSF samples from the lumbar cistern have been reported in some dogs [48]), as are spinal radiographic-myelographic studies, which help distinguish degenerative myelopathy from other degenerative conditions, such as pachymeningitis, disk protrusion, diskospondylitis, and spinal neoplasia. It has been reported that spinal cord evoked potentials recorded at the level of the cisterna magna, after stimulation of the sciatic nerve, are abnormal and that magnetic resonance imaging may reveal lesions throughout the spinal cord [58]. Despite the claims for immune-mediated disease (see above), repeated mitogen response assays in some dogs with confirmed degenerative myelopathy are negative [59]. Prognosis is guarded.

Recommended treatment involves a combination of exercise, vitamin supplementation, and administration of aminocaproic acid (EACA) (Amicar®, Lederle), at 500 mg, PO, tid [60]. This is the only drug that has been shown to alter the course of the disease, perhaps by blocking the final common pathway of tissue inflammation. It has been stated that EACA does not cure degenerative myelopathy but may slow its progression by as much as 50%, and that clinical improvement will usually be seen within 2 months of initiation of treatment [58]. Approximately 15 - 20% of affected dogs have no further deterioration, some improve, and others have survived for more than 4 years. The main disadvantage of this drug is its expense-it may cost from \$ 80 to \$100 per month. As an alternative, the generic injectable form of the drug (250 mg/ml) can be given as an oral solution by mixing 192 ml of EACA with 96 ml of a hematinic compound, e.g., Lixotinic. This combination provides 500 mg of EACA in 3 ml of the mixture. The dose of EACA in this form is 500 mg, tid. It is recommended that corticosteroids be reserved for acute exacerbations (e.g., prednisone, at 1 mg/kg/day, in three divided doses for 3 days before reducing to 0.33 mg/kg every 12 hours for 2 days, and continuing at maintenance levels of 0.5 mg/kg, every other day). High doses of vitamin E (2000 IU /day) and B complex vitamins (e.g., stress tablets, twice daily) can be given with the EACA. For pain, acetaminophen (i.e., Tylenol®) may be given at 5 mg/kg (not to exceed 20 mg/kg/day) [48]. Drugs that have no benefit include dimethyl sulfoxide, cobra venom, and immunosuppressive agents, such as cyclophosphamide and azathioprine. In conjunction with treatment, affected dogs should be placed on an increasing exercise program, including walking and swimming.

### **Encephalomyelopathy in Young Cats**

In a retrospective study, Palmer and Cavanagh have described a neurodegenerative disorder that primarily occurred in cat colonies (both conventional and specific pathogen-free) in the United Kingdom between 1969 and 1980 [61]. In some colonies, over 40 per cent of litters were affected. In this report, 19 cats aged 3 to 16 months developed neurological signs including hind limb ataxia that progressed to paraparesis, paraplegia, and in some instances, tetraparesis, along with urinary and fecal incontinence and muscle atrophy over the hindquarters. Other signs included visual deficits, dilated pupils, sluggish pupillary light reflexes, head shaking, head tremor, nystagmus, seizures ("fits"), and proprioceptive deficits. Spinal reflexes appeared intact, although the cutaneous trunci reflex was absent in some cats. Pain perception was also absent in one cat. Hematology and serum chemistries were normal. Serological testing for picorna virus, feline rhinotracheitis, feline pneumonitis, panleukopenia virus, and toxoplasmosis were negative. Transmission studies (animal and culture) were also negative. Plasma and red blood cell cobalamin levels were normal. Treatment of some cats with vitamin B12, at 0.25 mg/day for 6 weeks reportedly led to clinical improvement, although complete remission of signs did not occur.

Histopathological changes were confined to the CNS and characterized by Wallerian degeneration (degeneration of axons and myelin with myelophages often seen within remnants of the fiber) affecting long tracts in the spinal cord and variously in the brainstem, cerebral white matter, and optic pathways. There was an accompanying mild status spongiosis, increased numbers of astrocytes and microglial cells, and occasionally, swollen axons. Inflammatory changes were not a feature. Most severe lesions occurred in the spinal cord, especially involving larger diameter fibers (e.g., spinocerebellar and ventral tracts). There was no evidence of a distal dying back distribution to the lesions. All areas of the spinal cord were affected except the dorsal columns. In the brainstem, Wallerian degeneration was noted in the external arcuate fibers and caudal cerebellar peduncles, and less commonly in middle and rostral cerebellar peduncles, medial lemniscus, pyramidal tracts, spinal

trigeminal tracts, pontine decussation, medial longitudinal fasciculus, and cerebral peduncles. In 7 cats there was loss of Purkinje cells in the cerebellum and in 8 there was neuronal degeneration-loss in the spinal cord, especially in the intermediate cell columns, either at the base of the dorsal columns or in the region of Clarke's column. Larger ventral horn cells and larger neurons in the brainstem were usually not affected. No changes were found in peripheral nerves, spinal ganglia, or skeletal muscle.

The cause of this condition remains unknown. Genetic studies were inconclusive and nutritional and dietary toxins were ruled out. Despite the absence of inflammatory changes and the fact that no viral agent was isolated, the authors suggested the condition might have an infectious cause. Purkinje cell loss as well as spinal cord myelin degeneration and neuronal degeneration have been reported in young cats with feline panleukopenia virus [62] and the condition has some similarities to idiopathic feline polioencephalomyelitis. Another degenerative myelopathy with changes similar to those seen in the colony cats has recently been reported as a complication of chronic feline leukemia virus infection [63].

### **Encephalomyelopathy and Organic Acidopathies**

Several inherited diseases in people involve abnormal metabolism of organic and amino acids leading to neurologic dysfunction [195]. These conditions are rarely recognized in dogs and cats; however, methylmalonic and malonic aciduria has been reported in a young dog with progressive encephalomyelopathy (see cobalamin deficiency).

Two distinct autosomal recessive encephalopathic disorders with elevated urinary excretion of 2-hydroxyglutaric acid are recognized in infants and children: L-2-hydroxyglutaric aciduria and D-2-hydroxyglutaric aciduria [203-205]. Recently, a third variant has been reported associated with both isomeric forms of 2-hydroxyglutaric acid [206]. L-2-hydroxyglutaric aciduria is characterized by moderate to severe mental deficiency, often with cerebellar dysfunction, and epilepsy [203,207]. Magnetic resonance imaging typically reveals subcortical leukoencephalopathy, cerebellar atrophy, and signal changes in the putamina and dentate nuclei [203,208]. Increased levels of L-2-hydroxyglutaric acid also occur in blood and CSF. Patients may also have hyperlysineemia in plasma and CSF [203,209]. Patients with D-2-hydroxyglutaric aciduria have somewhat different clinical features (severe and mild phenotypes have been recognized), including dysmorphic facies, developmental delay, generalized hypotonia, myoclonic seizures, cortical blindness, and dilated cardiomyopathy [205,210]. The most consistent MRI finding is enlargement of the lateral ventricles (especially occipital); early MRI may demonstrate subependymal cysts and signs of delayed cerebral maturation. Later MRI may reveal multifocal cerebral white-matter abnormalities [211]. In addition, there lesions have been reported in the substantia nigra, the periaqueductal area, the medial part of the thalamus, the hypothalamus, the caudate nucleus, putamen and globus pallidus [212]. Patients typically have elevated levels of D-2-hydroxyglutaric acid in plasma and CSF, along with increased CSF levels of gamma-aminobutyric acid [213].

L-2-hydroxyglutaric aciduria has recently been reported in six Staffordshire Bull Terriers from 4 months to 7 years of age with clinical signs of seizures, ataxia, or dementia [214]. Cerebral MRI findings revealed a diffuse polioencephalopathy with hyperintensity on T2-weighted images of the cerebral, cerebellar, thalamic and brainstem gray matter. L-2-hydroxyglutaric acid levels were increased in urine, plasma and CSF. In all dogs tested, CSF lysine levels were also increased. One dog had increased urinary excretion of methylmalonic acid. CSF cytology/protein content was normal. Electrodiagnostic testing on muscle and nerve was normal as were muscle biopsies. While serum total and free carnitine concentrations were within the normal range, the concentrations of muscle total and free carnitine were reportedly low. Histopathology of the CNS has yet to be reported in affected dogs. The authors state that treatment strategies, pedigree analysis, and studies aimed at identifying the underlying biochemical defect are underway.

D-2-hydroxyglutaric aciduria has also been reported in an adult dog with a 2-year history of progressive lethargy and muscle weakness [215]. A neuromuscular component to this disease was suggested by abnormal spontaneous activity, including myotonic discharges (on EMG studies) and observation of scattered atrophic angular myofibers with increased lipid content in a muscle biopsy. Interestingly, muscle biopsy in one human patient with D-2-hydroxyglutaric aciduria demonstrated excessive glycogen histochemically and subsarcolemmal cylindrical spirals with normal mitochondria ultrastructurally [210].

### **Fibrinoid Leukodystrophy**

Fibrinoid leukodystrophy (synonyms include Alexander's disease and fibrinoid encephalomyelopathy) is a rare degenerative disorder that has been reported in two 8 month old male littermate black Labrador Retriever dogs, a 9 month old male Scottish Terrier, a 6 month old female Miniature Poodle, and a 13 week old Bernese Mountain dog [64-68]. Clinical signs are noted from 2 to 6 months of age and include pelvic limb paresis, progressive ataxia, wide-based stance, generalized weakness, exercise intolerance, reluctance to go up and down stairs, and sometimes tremors, falling, and personality changes, ranging from depression, agitation, and growling. In the Scottish Terrier, head tilt, seizure-like activity characterized by thoracic limb extension and opisthotonus, abduction of all limbs, and progressive tetraparesis were seen. At 9 months of age, the elbow and stifle joints of this dog were maintained in a flexed position with abnormally short range of motion, and attempts to ambulate resulted in a "swimming" motion [69].

Hematology, blood chemistries, urinalysis, and CSF analysis are normal. In the Scottish Terrier, an abnormal electroencephalogram was recorded, consisting of 50 to 75  $\mu\text{V}$ , 2 to 5 Hz wave forms [69]. Gross changes include gray pallor of cerebral subcortical white matter and sometimes, enlargement of the lateral ventricles. Histopathological changes include diffuse pallor with vacuolation of subcortical white matter with increased vascularity in which vessels are accentuated by thick cuffs of Rosenthal fibers, and mild to moderate gemistocytic astrocytic gliosis. There may be considerable myelin loss in some affected dogs [67], and neuronal loss may be evident in the cerebral cortex and subcortical gray structures [65]. The Rosenthal fibers are round, club-shaped, or elongated eosinophilic refractile bodies (up to 50  $\mu\text{m}$  in diameter) that are also found in astrocytes located in subependymal and subpial areas of the brain and spinal cord. These bodies are common in pontine and midbrain regions. In one immunohistological report, the Rosenthal fibers were positive for glial fibrillary acidic protein and  $\alpha\beta$ -crystallin [67]. Ultrastructurally, the refractile bodies consist of non-membrane bound granular osmiophilic aggregates within the cytoplasm of astrocytic processes adjacent to vessels. The aggregates are surrounded by bundles of glial filaments ranging in diameter from 7 to 10-nm, a size and morphology similar to that of glial fibrillary acid protein [66]. Scattered peripheral nerve fiber degeneration and demyelination were reported in one affected dog [68]. In skeletal muscle from this dog, multiple subsarcolemmal masses were noted in many muscle fibers and were basophilic on hematoxylin and eosin staining, bright red with Modified Gomori's Trichrome, black with NADH-TR, weakly periodic acid-Schiff positive, and brown with osmium tetroxide.

The histological, immunohistochemical, and ultrastructural findings in affected dogs appear identical with those in human cases [67]. The cause of this disease is not known, although the bodies may represent an overproduction of astrocytic fibers, and genetic or congenital disease has been postulated. In people, the condition is thought to represent an inborn error in astrocyte metabolism that leads to global dysmyelination or demyelination of the CNS [4]. The origin of the myelin loss is also unclear, but may be due to secondary damage to oligodendrocytes. Prognosis is poor. There is no treatment.

### **Hereditary Ataxia**

Hereditary ataxia is an autosomal recessive disorder in Smooth-Haired Fox Terriers in Sweden that has been reported as a clinical entity since 1941 [70,71]. A similar condition has been described in Britain and in Germany in Jack Russell Terriers, a short-legged variety of the Smooth-Haired Terrier breed [72,73]. In the German study, certain families of Jack Russell Terriers were predisposed to the disease [73]. Clinical signs in both breeds occur between 2 and 6 months of age when pelvic limb swaying and incoordination are observed. The incoordination progresses to involve all limbs and a prancing or dancing type of gait is observed, especially affecting the hind limbs. There is over protraction of the forelimbs. Animals appear to be unable to gauge the extent of a movement, which is unpredictable in direction. Severely affected animals frequently fall and are unable to rise again to their feet. Animals have difficulty in climbing stairs and jumping. There is no skeletal muscle atrophy. The head may show a rotational intention tremor, while hearing appears unimpaired. Approximately one third of the German cases have seizures and some dogs develop respiratory distress (Dr. Andrea Tipold, personal communication, 2001). Clinical signs may stabilize after several months and some affected animals are able to carry on a relatively normal life, in spite of the abnormal movements. In no case has the disease, per se, proved to be fatal [71].

Pathologically, a symmetrical bilateral myelopathy is found in the dorsolateral and ventromedial white matter of cervical, thoracic, and lumbar spinal cord [70]. There is myelin pallor reflecting Wallerian degeneration of the white matter, which has a spongy vacuolar appearance, accompanied by a mild subpial astrocytosis [10]. The dorsolateral spinal cord lesions appear to involve the spinocerebellar pathways [70]. In the Jack Russell Terriers, similar lesions are seen in the spinal cord but tend to be most severe in cervical segments (Dr. Andrea Tipold, personal communication, 2001). In addition, moderate diffuse gliosis, marked loss of myelinated nerve fibers, and argyrophilic axonal spheroids are found in central auditory pathways, including superior olivary nuclei, cochlear nuclei, connecting nerve fibers between these nuclei and the trapezoid body, and the lateral lemniscus [72]. Massive ballooning of myelin sheaths, with an apparently intact axon, was found in dorsal and ventral nerve roots and sciatic nerves, often accompanied by endoneurial edema and fibrosis and axonal swelling. In addition, marked nerve fiber loss and variable numbers of macrophages are found in the sciatic nerves [72].

Routine hematology and blood chemistries, urinalysis, CSF analysis, radiography, myelography, and spinal computed tomography are normal [70,73]. An abnormal measurement of brainstem auditory-evoked potentials (only waves I and II being detected) has been found in some affected Jack Russell Terriers [73]. There is no treatment. Control measures should focus on preventing further breeding of affected animals or their parents. Preliminary pedigree studies suggest a polygenic model of inheritance in Jack Russell Terriers [216].

### **Hereditary Polioencephalomyelopathy of Australian Cattle Dogs**

A vacuolar degeneration affecting primarily the gray matter in the CNS of young Australian Cattle Dogs has been described [74]. Male and female dogs were affected and clinical signs were noted within the first year of life. An initial presentation of psychomotor seizures (episodes of running in circles, vocalizing and urinating) was followed within approximately 6 to 12 months by progressive fatigue and thoracic limb stiffness, and eventual spastic tetraparesis over an ensuing period of several

months. Dogs in lateral recumbency could move their neck and trunk but thoracic limbs were rigidly extended in a tetanic posture with persistent contraction of extensor muscles. Dogs remained bright and alert. Patellar reflexes were depressed or absent in 2 dogs, but nociception and withdrawal reflexes were normal. In thoracic limbs, dogs felt a noxious stimulus applied but were unable to withdraw these limbs. While normal vestibular nystagmus was difficult to elicit, a brief positional nystagmus could be induced. Remaining cranial nerve function was normal. Routine blood cell count and serum biochemistry were normal. CSF analysis was normal in one dog but a mild increase in protein (29 mg/dl) and mild mononuclear pleocytosis (13 cells/ml) comprising leukocytes and macrophages, a few of which contained myelin fragments, was found in another dog. EMG studies showed evidence of continual muscle fasciculations in proximal thoracic limb muscles, rhythmic contraction of carpal flexors, and denervation potentials in numerous thoracic limb muscles.

Bilateral and symmetrical foci of malacia were seen grossly in the nuclei of the cerebellum and brainstem (caudal colliculi, lateral vestibular nuclei, lateral cuneate nuclei, and lateral reticular nuclei) and the gray matter of the spinal cord associated with cervical and lumbosacral intumescences. Additional, focal lesions were noted in the interpositional nucleus of the cerebellum and spinal nuclei of the trigeminal nerve. Bilateral atrophy of thoracic limb muscles was also found, being most severe in the scapular musculature. Microscopically, vacuolation of glial cells, dilation of the myelin sheaths and reactive astrocytosis characterized mild CNS changes and were seen in oculomotor, abducent, lateral cerebellar and hypoglossal nuclei, and the reticular formation. Dissolution of the neuropil, prominent vacuolation of reactive astrocytes, numerous glial fibrillary acidic protein-positive coiled astrocytic processes, neuronal vacuolation and loss with relative sparing of large neurons were observed in more advanced lesions. This change was most severe in the C7 - T1 region where tissue loss involved up to 80% of the spinal cord with relative sparing of only the central canal and a thin subpial band of white matter and substantia gelatinosa. The innermost area of the affected cord segments was characterized by advanced rarefaction. The next zone was filled with macrophages followed by a cribriform vacuolar zone and finally, the outer unaffected zone of white matter. Ultrastructurally marked mitochondrial accumulation and swelling were seen in astrocytes. Scattered Wallerian degeneration was found in ventral roots and peripheral nerves. In the appendicular muscles, changes interpreted as long-term denervation atrophy accompanied by widespread expression of the neonatal isoform of myosin were observed. The character of the neurological signs and the nature and distribution of the lesions within the CNS appear to be novel in veterinary neurology. A biochemical defect, possibly mitochondrial, affecting several cell populations within the CNS was proposed, with a more pronounced effect on glial cells than neurons. Genetic analysis suggested an autosomal recessive mode of inheritance.

### **Hound Ataxia**

A degenerative myelopathy has been recognized in Britain and Ireland in adult Foxhounds, Harrier Hounds and Beagles, of either sex [75-78]. In some packs, up to 75% of animals have been affected [77]. Age of onset varies from 2 to 7 years. Initial signs are pelvic limb weakness, ataxia and exaggerated elevation of these limbs when retracted at a gallop. Occasionally the pelvic limbs are dragged. The cutaneous trunci reflex is usually absent at levels caudal to T13 - L2 vertebrae. Muscle atrophy is not observed and spinal reflexes are normal. Affected animals usually become unworkable due to increasing pelvic limb incoordination within 6 to 18 months from the onset of symptoms. Animals remain bright and alert and thoracic limb function and cranial nerves are normal. In some affected dogs, clinical signs are not progressive. In one report, consanguinity was not established between affected dogs [78].

No gross lesions are observed. Histologically, severe Wallerian degeneration is found in the spinal cord involving all tracts except dorsal columns. Lateral columns are also unaffected in the cervical cord region. The degeneration, characterized by severe myelin ballooning with intramyelinic macrophages, is diffusely distributed within funiculi, varying in intensity from slight to severe. Axonal spheroids are rarely seen. The pathological severity seems unrelated to clinical neurological deficiency. Degeneration in lumbar cord is not as marked as in more rostral levels. In some animals, changes are most severe in the thoracic cord region. Typically, changes are not seen in gray matter of the cord, although chromatolysis was seen in neurons of the thoracic cord segments in one 2.5 year-old female Foxhound accompanied by astrocytosis and gliosis [77].

Tract degeneration extends into the brainstem, including the external arcuate fibers, inferior cerebellar peduncles, spinothalamic tract, medial longitudinal fasciculus, and tectospinal tract. At midbrain level, Wallerian degeneration is seen in the medial lemniscus, medial longitudinal fasciculus, decussation of the superior cerebellar peduncles, and rarely, the lateral lemniscus. With the exception of chromatolysis affecting neurons of the lateral vestibular nucleus in one Foxhound, there is no evidence of nerve cell damage or loss. No lesions are found in skeletal muscles, nerve roots or dorsal root ganglia, but in occasional animals, degenerative changes (possibly sensory) are found in sciatic nerves [77]. In one ultrastructural report, degenerate fibers were accompanied by astrocytic proliferation, and changes suggestive of a primary myelinopathy included vacuolated myelin sheaths around apparently intact axons, degenerative changes in inner oligodendrocyte tongues, large numbers of remyelinated axons with disproportionately thin myelin sheaths, and the occurrence of myelin lamellae around glial cells [78].

The etiology of this condition remains unknown although a dietary factor may be involved, since outbreaks typically occur in

animals kept under hunt condition where they are fed a diet consisting of paunch or tripe (the four stomachs of cattle and sheep), which has questionable nutritive value. Sheahan and colleagues suggest that the condition is associated with methionine deficiency and altered methionine synthetase activity [78] (see cobalamin deficiency). One outbreak in Beagles was attributed to pitch poisoning (dogs were eating the pitched lining of the kennels) [79], however, it is likely that this is another condition since the onset of signs was rapid, one affected dog was only 3 months of age, and in at least 2 cases, there was gradual recovery. Furthermore, no dogs were available for necropsy studies.

Results of hematological, radiographic, myelographic, and CSF testing are within normal limits. Serum copper levels are normal. In one report, mean serum methionine levels were significantly lower and mean liver methionine synthetase levels were significantly greater in affected dogs restored to a balanced diet than in age-matched controls maintained on the balanced diet [78]. However, methionine synthetase levels in spinal cord from affected animals were normal, as were liver folate concentrations [78]. To date, there is no specific treatment; however, the condition has been eliminated in kennels after the diet is changed to one containing a high proportion of meat [78,80].

### **Hypomyelination**

Over the past two decades, CNS hypomyelination has been reported in several breeds of dogs, some of which are known to be inherited. The condition has also been reported in cats.

#### **Hypomyelination in Chow Chows**

Hypomyelination of the CNS in Chow Chow dogs is believed to be hereditary [81,82]. Animals show clinical signs at 2 to 4 weeks of age-wide-based stance, "rocking horse" motion of the entire body when attempting to walk, hypermetria, intention tremors of head and limbs, and often, a bunny-hopping gait. Tremors decrease or cease completely when affected animals lie quietly or are asleep. Menace response is depressed bilaterally, however, vision and pupillary reflexes are normal. Clinical signs plateau from 6 to 12 months, followed by gradual improvement to the point where only a slight intention tremor is noted in some dogs, with other dogs appearing normal [82].

In these dogs, a severe myelin deficiency is found throughout the CNS, especially in subcortical white matter and foliate white matter of the cerebellum, as seen with myelin stains (e.g., Luxol fast blue). The outer half of the lateral and ventral columns of the spinal cord, the ventral half of the cerebral peduncles, parts of the optic tracts and several brainstem tracts such as spinothalamic and vestibular fibers are virtually devoid of myelin, with only a few single, widely separated myelinated fibers seen [81]. Axons appear normal and have thin or uncompacted myelin sheaths. Most axons in poorly myelinated areas are naked. Cell processes in contact with these axons appear to be derived from fibrous astrocytes and from large cells with abundant granular electron-dense cytoplasm, typical of oligodendrocytes, and containing astrocytic-type fibrils, a few profiles of rough endoplasmic reticulum, mitochondria, and many free ribosomes. No lesions are found in the gray matter. Peripheral and cranial nerves are myelinated normally. The myelin deficiency in absence of degenerative changes indicates a disorder of myelin formation rather than breakdown. Follow-up studies on older Chows revealed that myelination progressed with age but was still deficient at the age of 3 years [82]. Axons had thin or uncompacted myelin sheaths, separated by massive astrocytosis, and bizarre myelin formations. Conventional numbers of morphologically normal oligodendrocytes were found in the myelin-deficient areas. These results suggested that the condition in Chows dogs involved retarded myelination possibly due to a dysfunction or delay in oligodendroglial maturation [82].

#### **Hypomyelination in Lurcher Hounds**

A similar tremor syndrome and hypomyelinogenesis has been reported in two 4 week old, male, crossbred Lurcher Hound puppies [83]. Signs were first seen at 2 weeks of age and were characterized by pelvic limb bouncing or dancing while standing, along with fine tremors of the limbs and trunk, which sometimes involved the head. Tremors became more pronounced with excitement, abated with rest, and disappeared during sleep. Hypermetria was seen in the forelimbs in one puppy. Cranial nerve function, spinal reflexes, and postural reactions were normal. Clinical signs regressed completely in one puppy by 16 weeks of age.

Hypomyelination (based on pallor of myelin staining and abnormal myelin sheath:axon relationships) was present in spinal cord sections with numerous axons surrounded by inappropriately thin myelin sheaths, especially in the peripheral areas of the lateral funiculi of the cervical spinal cord. Some axons were naked. Small myelin figures were found in axons within oligodendrocytic and astrocytic processes. Demyelination was not seen. Oligodendrocytes and astrocytes appeared normal and there was no evidence of demyelination, lipophages, or inflammatory cells. Nerve roots and peripheral nerves were normal.

#### **Hypomyelination in Springer Spaniels**

A myelin disorder that has an X-linked recessive mode of inheritance has been reported between 2 and 4 weeks of age in male Springer Spaniels [84,85]. Tremors in Springer Spaniels ("shaking pups") are much more severe than those in Chow

Chows or Lurcher Hounds. Animals have great difficulty standing, performing useful coordinated movements, and cannot feed without assistance. A pendular nystagmus may be seen. Affected dogs are approximately half the size and weight of normal littermates. Seizures may occur as dogs mature. Most animals are euthanized as a result of progressive morbidity. Some heterozygous female puppies have shown a tremor at 12 - 14 days of age, which is not as severe as the affected males and which may disappear by 1 month [85].

Hypomyelination occurs throughout the CNS and it is more marked in the cerebrum and optic nerves than in the spinal cord. There is marked pallor of the white matter on gross examination of the CNS. Axons are either naked or surrounded by a disproportionately thin layer of myelin. Myelinated internodes tend to be short and heminodes are frequent. Vacuoles are present adjacent to axons or within glia but there is no evidence of demyelination. At the light microscopic level, many oligodendroglial and astrocytic nuclei are seen. Peripheral, cranial and autonomic nerves are myelinated normally. A marked transition from normal Schwann cell myelin to the amyelinated-hypomyelinated area of oligodendroglial territory is seen in dorsal and ventral nerve root entry zones. Ultrastructurally, there is marked distension of the rough endoplasmic reticulum (suggesting an abnormality of protein synthesis or transport) and perinuclear envelope in oligodendrocytes. Myelinated and non-myelinated zones are often found on a single axon. Many myelin sheaths appear poorly compacted and often show paranodal or internodal abnormalities suggestive of immaturity. Abnormal inter-relationships of oligodendrocytes and astrocytes are present at many paranodes [86] suggesting that astrocytic processes may interfere with oligodendrocyte-axon interactions [87]. A morphometric study revealed a marked reduction of oligodendrocytes in the affected pups [88]. Oligodendrocyte death was not noticeable. Astrocyte numbers were similar in both normal and affected pups. Axonal diameters were not reduced in the affected pups and there was no apparent correlation between myelination and axonal size in these animals. Total myelin volume and thickness were greatly reduced in the "shaking pups". Myelination appears to increase with age. Impaired stem cell division together with metabolic disturbance of oligodendrocytes was considered to be the main causes of the hypomyelination in this mutant [88]. Freeze-fracture studies indicated some abnormal contacts between oligodendrocytes and axons [89]. Biochemical studies have shown a reduction in various myelin proteins (myelin basic protein, myelin-associated glycoprotein, and 2' 3'-cyclic nucleotide phosphodiesterase, as well as proteolipid protein and the related DM-20 protein) and an immature form of myelin (the amount of the 21 kDa MBP compared to the 18 kDa MBP was relatively increased) in affected dogs [90,91]. Affected Springer Spaniel puppies carry mutations in proteolipid protein and DM-20, the major protein constituents of CNS myelin. These mutations reportedly hinder oligodendrocyte differentiation [92]. It has been reported that Schwann cells in shaking pups may penetrate the glia limitans and invade spinal cord, brainstem, and cerebellum and that this process increases with age [93]. Female heterozygotes of the shaking pup show myelin mosaicism of the optic nerve and spinal cord that is characterized by patches of normal central myelination interspersed between areas of amyelination or hypomyelination [85]. Abnormal oligodendrocytes with distended rough endoplasmic reticulum are found in the abnormal patches and are a marker of the trait.

### **Hypomyelination in Samoyeds**

This possibly inherited condition has been seen in puppies around 3 weeks of age [94]. Signs included generalized tremors (involving the head, eyes, trunk, and limbs), inability to stand, nystagmus (rapid spontaneous vertical or horizontal), and absent menace response. Tremors disappeared at rest or during sleep. Postural reactions, spinal reflexes, and nociception were normal. There was severe lack of myelin throughout the CNS, usually associated with reactive astrocytosis and diffuse staining for glial fibrillary acidic protein. The glia limitans appeared dense and thick with coarse astrocytic processes, especially in subpial and peripheral areas of the spinal cord. Staining for myelin basic protein was markedly diminished in hypomyelinated areas. Ultrastructurally, most axons were devoid of myelin, but occasional fibers were encircled by several poorly compacted lamellae, sometimes with accompanying astrocytic processes. Many naked axons were abutted by multiple astrocytic processes containing microtubules and intermediate filament bundles. Oligodendrocytes were greatly reduced in number (representing 13% of all glia counted compared to 57% in control pups). Furthermore, the oligodendrocytes were of the immature light or medium type and contained distended cisternae of endoplasmic reticulum and nuclear envelopes, similar to that seen in the shaking Springer Spaniels [88]. Lack of mature dark cells (these cells were present in the shaking Spaniels) suggested disruption in oligodendrocyte differentiation and maturation, as has been reported in the shaking Spaniels [88,92]. There were increased numbers of astrocytes and microglial cells (type III glial cells). Peripheral nerves were myelinated normally.

### **Hypomyelination in Weimaraners**

American Weimaraner puppies of either sex affected by hypomyelination develop generalized body tremors and dysmetria about 3 weeks of age [95]. Mental status, gait, postural reactions, vision, and cranial nerve and spinal reflexes are normal. Signs appear to ameliorate with age, so that dogs may be clinically normal by one year of age. Many axons throughout the brain and spinal cord are either hypomyelinated or amyelinated relative to controls.

Hypomyelination is especially prominent in peripheral subpial regions of the spinal cord, particularly of the ventral and lateral funiculi. In contrast, dorsal columns appear normally myelinated. Myelin is normal in nerve roots and peripheral nerves. In hypomyelinated areas, astrocytes outnumbered oligodendrocytes that have features typical of medium or dark cell types. Ultrastructurally, some myelin sheaths are uncompacted while many axons are being actively myelinated. There is no evidence of oligodendrocyte necrosis. Neuronal cell bodies are normal. A reversible defect in glial differentiation is considered responsible for the hypomyelination.

A condition has been reported in the UK in an 8 week old Weimaraner puppy with signs of incoordination, pelvic limb weakness and ataxia, bunny-hopping gait when attempting to move quickly, and abnormal frog-like sitting posture [96]. A tremor was not seen. There was no muscle atrophy in the limbs. There was subpial depletion of myelin throughout the spinal cord, involving all funiculi. Pial thickening and vacuolated degeneration of the sensory neurons in the dorsal horns and of neurons in the lateral cuneate nucleus and in the lateral caudal part of the reticular formation in the medulla accompanied this change. Dystrophic axons were present in the spinal cord, granular layer of the cerebellar vermis, and internal capsule. While focal vacuolation was seen in the cerebellar white matter, there was no myelin depletion found in the brainstem, cerebellum or cerebral hemispheres. No abnormalities were seen in nerve roots, dorsal root ganglia or in peripheral nerves. Despite the clinical and pathological differences, the condition in this puppy may be a variant of the disorder described above in the American Weimaraners.

### **Hypomyelination in Bernese Mountain Dogs**

Clinical signs of central hypomyelination appear in Bernese Mountain Dog puppies of either sex from 2 to 8 weeks of age [97] and are manifested as a fine tremor of the limbs and head which becomes more intense with excitement or stress and which disappears with sleep. Other signs are weakness, imbalance, a high tail carriage, and a stiff action of the pelvic limbs. Signs appear to gradually diminish with age but tremors may reappear when animals are frightened or excited.

Hypomyelination, characterized by presence of thinly myelinated axons, is observed throughout the spinal cord but not in the brain. There is astrocytosis and an increased number of astrocytic processes. Oligodendrocytes appeared normal, except for a small number (approximately 5%), which contained abnormal dilated membrane systems, membranous whorls and osmiophilic structures. Peripheral nerves are myelinated normally. Preliminary breeding data suggest an autosomal recessive mode of inheritance.

### **Hypomyelination in Dalmatians**

Cerebrospinal hypomyelinogenesis has been reported in a 5 week old Dalmatian puppy [98]. Generalized body tremors were present at birth. The puppy could not walk voluntarily and horizontal pendular nystagmus was observed. The tremors disappeared at rest and during sleep. Spinal reflexes were normal. Grossly, on frontal sectioning of the brain and spinal cord, poor demarcation between the gray and white matter was noted. Microscopically, myelin was not found anywhere in the CNS, although normal axons were demonstrated with silver stains. Disseminated spongy vacuolation was found in the white matter of the spinal cord. There was no evidence of active white matter degeneration. Ultrastructurally, there was prominent astrocytic gliosis throughout the white matter. Cells, with features typical of oligodendrocytes, appeared reduced in number. Most nerve fibers were entirely devoid of myelin, but occasional larger axons were covered by a thin irregular layer of 2 or 3 myelin lamellae. Abnormal myelin inclusion figures were noted in some oligodendrocytic processes. Limited axonal necrosis was found throughout the white matter. The peripheral nerves were myelinated normally. A failure of myelin synthesis was considered the primary cause of this disorder.

### **Hypomyelination in Cats**

Hypomyelination of the CNS has been reported in two Siamese kitten littermates [99]. Signs began at 4 weeks of age and were characterized by a history of progressively intensive whole body intention tremors accompanied by episodes of frenzied behavior with indiscriminate biting. The kittens assumed a quiet (normal) state at rest, but with activity, the above-mentioned signs returned. Microscopic examination of spinal cord revealed marked hypomyelination, as suggested by pallor of white matter of the lateral and ventral funiculi, without apparent rostrocaudal gradation in severity. The dorsal columns appeared normal, as did nerve roots and spinal ganglia. Silver staining showed morphologically normal axons. The brainstem, cerebellum, and cerebral cortex appeared normal. Glial fibrillary acidic protein staining confirmed a mild astrogliosis, including an increased prominence of the glia limitans in the hypomyelinated areas, with astroglial processes often assuming a radial orientation. Ultrastructurally, there was a preponderance of nonmyelinated axons and the few myelinated sheaths that were present appeared thin and frequently loosely compacted. Astrocytic processes often had condensed intermediate filaments. Immunocytochemically, the intensity of staining for myelin basic protein, myelin-associated glycoprotein, and proteolipid protein was decreased in the hypomyelinated areas, reflecting the increased numbers of hypo- or amyelinated axons.

Note that frenzied behavior and biting is unusual for hypomyelination and may represent paresthesia evoked by inappropriate



excitation of noninsulated portions of sensory pathways [99].

### **Miscellaneous Hypomyelination**

Note that various forms of CNS hypomyelination have been reported in several lysosomal storage diseases, including globoid leukodystrophy in dogs and mannosidosis in cats.

### **Idiopathic Vascular Calcification**

A novel degenerative disease has recently been reported in a 3 month old Labrador Retriever puppy [196]. Clinical signs included progressive lethargy, weakness, and reluctance to move over a three day period. Examination revealed generalized muscle atrophy and palpably hard muscles. Joints were enlarged and painful and there was restricted range of joint and spinal movement. The dog showed slight ventroflexion of the head, neck stiffness, and was tetraparetic with proprioceptive deficits in pelvic limbs. All spinal reflexes were diminished. Radiographic studies showed multifocal mineralization throughout the body including intervertebral disks, cartilage of spinous processes, intersternbral and costal cartilages, growth plates, articular/periarticular soft tissues (joint capsules, muscle/tendon insertions), menisci, and thyroid, cricoid and extrathoracic tracheal cartilages. In addition, mineralization was noted in the common carotid arteries, tongue and kidney vessels, and vessels in the popliteal region. Sonography confirmed mineralization of neck and kidney arteries. EMG studies indicated presence of fibrillation potentials in paraspinal and limb muscles while nerve conduction was slow in the peroneal nerve. Grossly, carotid and coronary arteries were extremely hard and thickened by mineral deposition. Microscopic changes included marked mineral deposition in the tunica intima and tunica media of blood vessels in several organs, as well as in carotid and coronary arteries. The mineralization in periarticular tissue and joint capsules was accompanied by a granulomatous reaction with numerous multinucleated giant cells. In cervical and thoracic spinal cord segments, a myelopathy characterized by fragmentation and loss of axons and myelin ballooning/macrophage phagocytosis was found in all white matter funiculi. Multifocal subdural calcifications were seen at all levels of the spinal cord. Swollen axons and partial myelin loss was found in the peroneal nerve while calcifications were noted in perineurial vessels of the radial nerve. Atrophy and hypertrophy were present in skeletal muscle. No histological abnormalities were observed in the brain. The cause of the calcifications was not determined. Additional diagnostic testing revealed that serum parathormone, vitamin A, 25-hydroxycholecalciferol (25-OH-VitD), and 1,25-dihydroxycholecalciferol (1,25-OH-VitD) were normal. In addition, screening for mucopolysaccharidoses did not indicate storage disease. The authors suggested that this unusual condition had similarities to idiopathic arterial calcification of infancy seen in children, a rare disorder characterized by extensive arterial calcification and stenoses of large and medium-sized arteries with complications including severe systemic hypertension and cardiomyopathy [197].

### **Kooiker Dog Myelopathy**

A degenerative myelopathy has been reported in young Kooiker dogs (Dutch decoy dogs), of either sex, with signs beginning from 3 to 12 months of age [11,100]. Clinical signs include mild to severe hind limb paresis and ataxia. In some dogs, forelimbs are similarly affected and there may be proprioceptive deficits, exaggerated spinal reflexes, and urinary incontinence. Many dogs are euthanized by 12 months of age. Routine hematology, blood chemistries, radiography, and myelography are normal. Grossly, lesions are found at all levels of the spinal cord, and are seen as transparent areas associated with malacia and loss of myelin and axons. Lesions appear most severe in the last cervical and first thoracic cord segments, being localized primarily in ventral and dorsal columns. The ventral malacic areas extend to involve lateral columns in some cervical and thoracic segments. In severely affected dogs, all white matter may be involved in some thoracic segments. There is reactive vascular proliferation, numerous macrophages, and variable numbers of gemistocytic astrocytes in the malacic areas. At the border of the necrotic areas, axons appear intact. Wallerian degeneration occurs in spinal cord segments caudal to the ventral and lateral malacic areas, and rostral to the dorsal areas of malacia. Spinal cord neurons and nerve roots are not affected. Wallerian degeneration in the dorsal funiculus sometimes extended to the gracile and cuneate nuclei. Severe neuronal degeneration may occur in trapezoid body, while vacuolation is sometimes seen in the olivary nuclei. Pedigree studies suggest this disease has a simple autosomal recessive mode of inheritance. This condition is quite similar clinically and pathologically to Afghan hound myelopathy except for the reported axonal involvement in the Kooiker dogs [2].

### **Labrador Retriever Axonopathy**

A degenerative disorder has been reported in Labrador Retriever puppies characterized by an ataxic-dysmetric gait when they first begin to walk [10]. The hind limbs move in a crouched, short-strided, adducted manner while the forelimbs are hypermetric. Animals may fall frequently. Forelimbs become progressively more spastic and abducted. By 3 to 5 months of age, most puppies are unable to stand or walk without assistance. Signs may remain static after this time. Head tremor occurs late in the course of the disease. Hematology, blood chemistries, and CSF analysis are normal.

Grossly, all affected puppies have aplasia or hypoplasia of the corpus callosum. Spina bifida at C7 has been found in two puppies. Microscopically, there is extensive bilaterally symmetrical degeneration of the spinal cord white matter, particularly in the superficial dorsal areas of the lateral funiculi, the fasciculus gracilis of each dorsal funiculus, and the ventral funiculus adjacent to the ventral median fissure. The degenerative changes are most severe in the thoracic cord segments, with decreasing intensity in the lumbar and cervical segments. Degenerative changes of partial or complete axonal and myelin loss and associated gliosis are found throughout the medulla oblongata, caudal cerebellar peduncles, and cerebellum. Ultrastructural studies indicate a more extensive loss of larger caliber axons with preservation of smaller processes. There is multifocal presence of swollen axonal spheroids that contain neurofilaments, vesicular structures, mitochondria, and Golgi apparatus. The spheroids appear most numerous in the dorsal funiculus of the cord at all spinal levels, on the lateral surface of the medulla, and in focal areas of the granular layer of the cerebellar cortex. They occur with less frequency in the foliate and central cerebellar white matter, transverse fibers of the pons and middle cerebellar peduncles, optic tracts, internal capsule, and corona radiata of the cerebrum. There is extensive neuronal loss in spinal ganglia and spinal cord gray matter. Degenerative changes are found in each olivary nucleus characterized by neuronal chromatolysis and scattered large spheroids. In some dogs, there is complete loss of cell bodies in these nuclei with astrocytic replacement. This degenerative disorder is presumed to have an inherited recessive mode of inheritance [10].

### **Lafora's Disease**

A progressive, degenerative neurological disorder associated with a complex glycoprotein accumulating within neurons and glial cells or lying free in the neuropil has been recognized sporadically in dogs for several decades. The condition is considered analogous to Lafora's disease in people in whom it is clinically characterized by progressive myoclonic epilepsy. Most reports involve older Beagles and Basset Hounds. Clinical signs are variable, including depression and somnolence [101]; however, seizures (e.g., myoclonic epilepsy, see Epilepsy) are often reported in advanced stages of the disease, and have been noted in affected dogs from 5 months to 7 years of age [102-107].

Seizures can be precipitated by external stimuli, especially a change in noise or light in the surroundings [103,107]. Electroencephalographic studies may reveal slow, rhythmic activity with showers of myoclonic type seizure patterns [107]. In a 10 year old female Corgi, clinical signs progressed from abnormal, jerky head movements to generalized muscle fasciculations with severe myoclonic contractions of the head and neck muscles [102]. Almost identical signs (body tremors, twitching, and/or abnormal jerky head movements) have been observed in Miniature Wirehaired Dachshunds in the United Kingdom [198] and in South Africa [199]. The myoclonic jerks occurred spontaneously or in response to visual or auditory stimuli, or sudden movement, but did not appear to affect consciousness. In one study, generalized seizures and hypnic jerks were also reported [198]. Apart from these signs, neurological examination was normal in these dogs, as were hematology and serum chemistries (except for mild increase in CK and lactate dehydrogenase levels in some instances), CSF analysis, and cranial magnetic resonance imaging. EMG studies may be normal [198] or show evidence of moderate amounts of fibrillation potentials and positive sharp wave activity [199]. Muscle biopsy may reveal presence of an amorphous bubbly subsarcolemmal material consisting of periodic acid-Schiff positive, diastase resistant inclusions (polyglucosan bodies) [105,198,199]. The inclusions also stain positively with Grocott's methenamine silver nitrate. Similar inclusions may be found in peripheral nerves [198]. The ultrastructural characteristics are similar to those inclusions found in the CNS (see below).

In most reports to date, variably sized, basophilic inclusions have been observed in perikarya and processes of neurons throughout the brain and spinal cord, and are often especially numerous in neurons within the cerebrum, cerebellum, thalamus, and midbrain [101-104,106,107]. The inclusions are strongly positive for carbohydrate stains, weakly metachromatic, and lipid negative [101,103]. The histological, immunohistochemical, and ultrastructural features of polyglucosan bodies in humans and Lafora bodies in dogs are similar [108]. Lafora bodies in dogs stain with concanavalin A indicating they contain mannose and glucose residues and suggest a derivation from rough endoplasmic reticulum and Golgi [109]. Occasionally, they are also seen in retina, peripheral nerves, liver, spleen, and lymph nodes. In skeletal muscle, inclusions that stain dark blue with hematoxylin and eosin, and red with periodic acid-Schiff (PAS), may be seen lying between myofibers or beneath the sarcolemma [103,105]. Based on differences in internal structure and staining characteristics, three types of Lafora bodies are recognized [104]:

1. Type I - Small (3 to 10  $\mu\text{m}$  in diameter), fine, evenly stained granules. This is the most common type and is usually found in middle and deep layers of the cerebral cortex and in glial cells of the cerebellum. Ultrastructurally, these bodies consist of branching fibrillar structures without a limiting membrane. The branching filaments measure about 8 - 10-nm in diameter [110].
2. Type II - These larger bodies (13 to 30  $\mu\text{m}$  in diameter) have a strongly PAS-positive homogeneous core with a more faintly staining radiating periphery. This form is commonly found in Purkinje cells of the cerebellum and in the midbrain. Electron microscopy reveals osmiophilic granules in a central core surrounded by fibrillar material. Rough

endoplasmic reticulum in affected neurons may be dilated with increased numbers of coarse ribosomes free in the cytoplasm. Such changes suggest abnormalities in protein synthesis.

3. Type III - These bodies range from 5 to 20  $\mu\text{m}$  in diameter and are occasionally found in the midbrain. These structures exhibit a dense peripheral ring of PAS-positive material.

The relationship between seizures and these Lafora bodies is enigmatic since similar inclusions have been observed in the CNS of older dogs (e.g., over 8 years of age) of various breeds with no signs of seizures [101,110-112]. These bodies may also be found in the retina of clinically normal dogs and cats [113]. Furthermore, in a recent study of epilepsy-prone beagles only 6 of 68 dogs (8.8%) had Lafora-like inclusion bodies [114].

Lafora bodies have also been found in cats. In a recent report, Lafora bodies were identified in the brain of a young adult cat with neurological signs characterized by intermittent but progressively worsening head and body tremors [115]. The cerebellar cortex was the most severely affected area of the brain and the deposits were identified within Purkinje cell bodies and processes and throughout the neuropil. More commonly, Lafora bodies occur in the CNS of aging cats, without signs of seizures, as incidental lesions [116]. In one feline study, most of the bodies were situated in the neuronal processes and disseminated throughout the brain, especially in the cerebral cortex, midbrain, cerebellum and medulla oblongata [117]. In the spinal cord of older cats and dogs, caudal lumbar and the coccygeal regions are reportedly predilection sites for Lafora bodies, being prominent in the ventral column and intermediate substance and preferentially located in neuronal processes, but only rarely in astrocytes. [118].

Prognosis is somewhat guarded in animals with Lafora's disease because of the tendency for signs to become progressively worse; however, this may not be the case for at least some affected Miniature Wirehaired Dachshunds [198]. In people, Lafora's disease is an autosomal recessive, progressive myoclonus epilepsy with characteristic inclusions (polyglucosan bodies) caused by mutations in the EPM2A gene, which codes for laforin, a cell membrane and endoplasmic reticulum-associated protein, tyrosine phosphatase, that may play a role in the prevention of polyglucosan accumulation in healthy neurons [200,201].

### **Miniature Poodle Demyelination**

A rare, possibly inherited, neurodegenerative disorder has been reported in Miniature Poodles [119-121]. Clinical signs first appear between 2 and 4 months of age with some puppies showing signs of ataxia-dysmetria with constant shifting of the hind limbs and difficulty standing. Puppies may fall frequently trying to reach their food bowl. Within 1 to 2 weeks, puppies develop a spastic paraplegia followed rapidly by a tetraplegia [119,120] and tend to lay on their sides with all limbs extended, sometimes with the forelimbs held in a clasped position [120]. Placing and hopping reactions are absent, while spinal reflexes are usually intact, cranial nerve function is normal, and puppies remain alert. Hand feeding may be necessary and some puppies appear to have impaired tongue function. In one report, grinding of the teeth was a constant signs [121]. Loss of sensation to pinprick caudal to the scapula was noted in another affected dog [119]. Hematology, blood chemistries, urinalysis, and radiography are within normal limits. CSF analysis is usually normal, although a mild protein increase was noted in one dog [121].

Microscopically, large areas of malacia occur in the midbrain and the cervical cord [119]. In the midbrain, there is a symmetrical loss of myelin in the tegmentum. Areas of malacia also occur bilaterally in medial and lateral lemniscus, inferior colliculus, cerebral peduncles, posterior commissure, corpus callosum, middle cerebellar peduncle, roof of the cerebellum, descending vestibular tract, and pyramids [119]. In the cord, the most severe lesions occur in dorsal and ventral white columns of cervical and thoracic segments [121]. Loss of myelin may be almost complete at C7 with only the fasciculus proprius being spared, while there is some preservation at C2 and T5, and only slight loss at the lumbar intumescence [119]. The dominant lesion appears to be distinct myelin degeneration and loss. In the center of the malacic lesions, nerve cells are preserved, although some show evidence of chromatolysis. There is some hyperplasia of small vessels with endothelial swelling, a microglial reaction, and variable astrocytosis. In some areas, lipid macrophages are common. A status spongiosis is found at the periphery of the malacic lesions with myelin ballooning. Silver stains reveal loss and degeneration of axons in some areas, but with some degree of axonal integrity in others [121]. Gray matter in the spinal cord is preserved, as are dorsal and ventral nerve roots. Prognosis is poor. There is no treatment. To my knowledge, there have been no additional reports of this disease during the past 20 years. Summers and colleagues reported that 2 cases had been seen at Cornell over the course of 30 years [3].

### **Mitochondrial Encephalomyelopathy**

A progressive encephalomyelopathy of insidious onset has been reported in a 16-month-old female English Springer Spaniel [122]. Clinically, the dog showed evidence of ataxia-dysmetria that was exacerbated by excitement, occasionally stumbled into objects, and had mild behavioral abnormalities, including moments of disorientation and being easily excitable. A vertical positional nystagmus could be elicited and postural reactions were delayed and spastic in all limbs. Patellar reflexes

were brisk and there was no evidence of muscle atrophy. Routine laboratory findings, including CSF analysis, were normal. Grossly, bilateral and symmetrical depressed gray foci were observed in the dorsal accessory olivary nuclei. Light microscopic findings included profound Wallerian degeneration (diffuse axonal and myelin loss) and astrogliosis of the optic pathways (bilaterally), loss of Purkinje neurons along with Bergmann's gliosis, granular cell layer torpedoes, and axonal spheroids and gliosis in cerebellar nuclei (bilaterally), focal bilateral and symmetrical brainstem spongiosis (olivary nuclei and substantia nigra) and diffuse neuraxial astrogliosis with swollen and abnormally shaped nuclei in the above-mentioned sites as well as in the lateral geniculate nuclei. The majority of neurons in the brain and spinal cord appeared normal. Variable, scattered Wallerian degeneration was found in all white matter funiculi of the spinal cord and peripheral nerves, especially the sciatic. Ultrastructurally, there were giant (up to 10 times normal size) and bizarre mitochondria (e.g., increase or loss of mitochondrial cristae, membrane blebbing, and internal compartments) within neuronal perikarya and axons as well as diffuse loosening of the cerebral and cerebellar neuropil associated with myelin sheath ballooning and/or astrocytic intracellular edema. It was suggested that the neuropathological findings in this dog resembled the mitochondrial encephalomyopathies of man.

### **Motor Neuron Diseases**

Motor neuron diseases are neurodegenerative disorders in which there is premature degeneration and death of various neuronal cell populations in the spinal cord and/or brainstem, and as such, can be classified among the degenerative abiotrophies [1]. In small animals, most of the conditions involve the spinal cord lower motor neurons and, based on comparative studies, have also been termed spinal muscular atrophies. Most of these degenerative conditions occur within the first 3 to 6 months of life. Motor neuron diseases have been reported in several breeds of dogs, in which they have a familial or genetic basis, but are only rarely seen in cats. Clinical signs usually are progressive and tend to be dominated by neuropathies in pelvic and thoracic limbs as a consequence of lower motor neuron (LMN) involvement. Prognosis is guarded to poor, and there is no treatment.

### **Motor Neuron Disease in Giant-Breed Crosses**

This rare degenerative condition, also known as Stockard's paralysis, was produced in 1936 by crossbreeding Great Danes with Bloodhounds and St. Bernards [123]. Clinical signs occur around 3 months of age and are characterized by sudden onset of paresis and posterior paralysis, priapism, and atrophy of pelvic limb appendicular muscles. There is no involvement of head, neck, or trunk. No additional reports have appeared in the literature since 1936. Pathological findings include chromatolysis, degeneration, and depletion of motor and preganglionic sympathetic neurons in ventral and intermediolateral horns of lumbar spinal cord. The disease is transmitted through an inheritable, multiple factor involving at least three dominant genes.

### **Motor Neuron Disease in Swedish Lapland Dogs**

An autosomal recessive disease has been reported in Swedish Lapland dogs [124] that has been compared to infantile spinal muscular atrophy (Werdnig-Hoffman disease) in children [124]. I have listed this condition with the multisystem neuronal abiotrophies.

### **Motor Neuron Disease in English Pointers**

A LMN degenerative disorder has been described in young English Pointer dogs in Japan [125] that appears to have an autosomal recessive mode of inheritance [126]. Clinical signs of pelvic limb trembling (an initial sign), weakness, dysphonia, and diminished tendon reflexes are observed in affected dogs at about 5 months of age. Progressive muscular atrophy occurs in all limbs and trunk, particularly in the shoulder region. Animals eventually become tetraplegic, with superficial muscle fasciculations seen and eventually, joint contractures. Electromyographically, fibrillation potentials and positive sharp waves are noted in epaxial, proximal, and distal appendicular muscles, but are first seen in distal muscles [127]. The clinical course of this progressive disease is 3 to 4 months. Routine hematology and radiography are normal.

Axonal degeneration is found in peripheral nerves and chronic neurogenic atrophy and endomysial fibrosis occur in skeletal muscle. While the number of ventral horn cells in the spinal cord seem to be normal, numerous accumulated lipid-like granules, 1 to 3  $\mu\text{m}$  in diameter, are present in ventral horn cells and in hypoglossal and spinal accessory nuclei of the brainstem. These granules stain with Nile blue sulfate, Sudan black B, Luxol fast blue, Alcian blue, and periodic acid-Schiff on paraffin sections, suggesting the granules are composed of a compound lipid. The granules have no autofluorescence. Ultrastructurally, granules appear as multi-lamellar structures, arranged concentrically or in parallel, resembling membranous cytoplasmic bodies or zebra bodies. This finding suggests that a hereditary abnormality of lipid metabolism may underlie the LMN disease in these dogs [125].

### **Motor Neuron Disease in German Shepherds**

A focal form of spinal muscular atrophy has been reported in two German Shepherd puppies [128]. Signs were seen 2 weeks after birth and were characterized by unilateral or bilateral thoracic limb weakness and atrophy, carpal valgus deformity, and carpal flexion due to contracted, atrophic flexor muscles. In one puppy, signs progressed rapidly over the ensuing 5 weeks to the point he was unable to stand or walk using the thoracic limbs. Electromyographic studies revealed fibrillation potentials and complex high frequency activity in shoulder, forearm and interosseous muscles, bilaterally. Microscopic changes included asymmetric loss and degeneration of motor neurons in the cervical spinal cord intumescence (from C5 to T1), especially in the lateral region of the ventral horn of C7 - 8. Degenerating neurons appeared vacuolated or chromatolytic. Glial nodules, neuronophagia, and axonal spheroids were seen occasionally. Degenerative changes, including axonal loss and multifocal presence of Bungner's bands (denervated Schwann cells), were observed in ventral rootlets and in thoracic limb peripheral nerves, and neurogenic atrophy was seen in muscle. Ultrastructurally, numerous denervated Schwann cells were seen together with dispersion and loss of ribosomes, and variable cisternal dilation in some degenerating neurons. The peripheral chromatolysis resulted from dispersion and loss of the free and attached ribosomes that normally form Nissl bodies. Prognosis is guarded. Surgical tenotomy and carpal splinting were effective in the second dog, which was clinically less affected. At 15 months of age, thoracic limb atrophy was not seen in this dog, although slight weakness was sometimes observed. This canine condition is thought to resemble the asymmetric and unilateral, benign spinal muscular atrophies found in people.

### **Motor Neuron Disease in Doberman Pinchers**

Motor neuron degeneration has been documented in 2 male Doberman puppies from a litter of eight [10]. Signs of pelvic limb weakness were seen around 4 weeks of age and progressed to tetraparesis and muscle atrophy in all limbs. Microscopic changes showed degeneration of neurons in spinal cord and various brainstem nuclei, including vestibular and reticular nuclei. The neurons were chromatolytic or vacuolar, the latter change apparently being derived from rough endoplasmic reticulum.

### **Motor Neuron Disease in Griffon Briquet Vendéens**

Motor neuron disease characterized by progressive weakness, hind limb paresis and eventually tetraparesis (extensor paralysis in hind limbs, flexor paralysis in forelimbs) was documented in two 2 month old Griffon Briquet Vendéen dogs from a litter of six [202]. Muscle atrophy was prominent in all limbs, with diminished spinal reflexes and loss of superficial and deep pain sensation. Mental status and cranial nerve function were normal. Microscopic lesions included marked neuronal loss in ventral horns cells of the spinal cord, Wallerian degeneration of ventral spinal roots and peripheral nerves, and neurogenic muscle atrophy. Axonal swelling was noted adjacent to neuronal cell bodies. In addition, a severe loss of motor neurons was observed in the red nuclei and in lateral and medial vestibular nuclei accompanied by astrogliosis.

### **Motor Neuron Disease in Salukis**

A motor neuron abiotrophy was reported in a 9 week old Saluki puppy presented for progressive generalized weakness and bilaterally symmetrical deformities of the carpi associated with limb contracture [236]. Histological lesions included diffuse, symmetrical, degenerative lower motor neuronopathy of the ventral horn of the spinal cord characterized by neuronal swelling, chromatolysis, swollen dendritic processes and enlarged axons. Degenerative changes were present in ventral nerve roots. No lesions were seen in spinal ganglia or brainstem nuclei. Similar clinical signs were noted in a sibling.

### **Motor Neuron Disease in Other Canine Breeds**

A LMN disease has been reported in New Zealand in 9 dogs (6 rural collie sheep dogs, a Pug, a Dachshund, and a Fox Terrier. Seven of the dogs were 3 to 9 months of age) [129]. Clinical signs included acute onset of posterior paresis that typically progressed rapidly (over 2 to 4 weeks) to posterior flaccid paralysis and, in 3 dogs, to tetraplegia. Severe muscular atrophy occurred in pelvic limbs and, in a few animals, in all four limbs. Microscopic lesions were found in thoracic and lumbar cord segments in dogs with pelvic limb signs and were also present in cervical cord segments in tetraplegic dogs. Lesions were characterized by mild to marked loss of motor neurons in lateral and ventrolateral regions of the ventral horn of the spinal cord (often seen as empty spaces), and often accompanied by diffuse microgliosis and several small glial scars in areas of missing motor neurons, and presence of Wallerian degeneration in ventral spinal roots and spinal nerves. The peripheral nerve changes appeared more severe in distal levels. Minimal changes were seen in dorsal roots or dorsal root ganglia. The cause of the LMN disease was not established.

### Motor Neuron Diseases with Neurofibrillary Accumulation

Several motor neuron disorders have been described in which there is accumulation of neurofilaments in neurons. The best studied is hereditary canine spinal muscular atrophy (HCSMA), a dominantly inherited, LMN disease in **Brittany Spaniels** that does not appear to be sex linked [130-132] and which has certain clinical and pathological features in common with familial amyotrophic lateral sclerosis in people [133]. Three forms of the disease have been recognized-accelerated, intermediate, and chronic [134]. The accelerated disease appears in puppies that are homozygous for the trait; whereas, heterozygous animals express intermediate and chronic phenotypes [132].

- a. Early Onset or Accelerated Disease - This form of the disease is similar to spinal muscular atrophy of infants (spinal muscular atrophy type I or Werdnig-Hoffman disease [135]). Puppies first show clinical signs by 6 to 8 weeks of age. Affected puppies are usually thinner than littermates, develop weakness associated with paraspinal and proximal pelvic limb muscular atrophy, and often have a slow tremor of the head. There is weakness of muscles of mastication and the tongue, which makes feeding difficult, and the gag reflex may be depressed. Affected dogs become tetraparetic or tetraplegic and are unable to lift their heads by 3 to 4 months of age. They lose about 30% of their body weight due to neurogenic muscle atrophy. Pathological findings occur in motor neurons of the ventral horns of the spinal cord and certain brainstem nuclei, especially the hypoglossal, and include chromatolysis, variable dendritic enlargement, and swollen axons in gray matter of spinal cord, and sometimes, in proximal portions of the ventral root exit zone or proximal ventral roots. Proximal axons are filled with massive accumulations of 10-nm maloriented intermediate neurofilaments, an abnormality similar to that which occurs early in the course of human amyotrophic lateral sclerosis [130,133]. Many myelin sheaths around distended axons are attenuated.
- b. Intermediate Disease - This is the most common form of the disease [2] and is similar to juvenile spinal muscular atrophy of children (spinal muscular atrophy type III or Kugelberg-Welander syndrome [135]). Clinical signs develop by 6 to 12 months of age, and are characterized by weakness in proximal muscles of limb girdles and trunk. Animals walk in a waddling fashion. Progressive atrophy ensues in proximal muscles of pelvic limbs and lumbar paraspinal muscles. Intercostal muscle involvement may lead to respiratory distress. Affected dogs are usually unable to walk by 2 to 3 years of age. Microscopic findings reveal loss of motor neurons late in the disease, fewer axonal swellings than those seen in the accelerated disease, and neuronophagia in ventral horn neurons. Ultrastructurally, there may be electron-dense, membrane-bound, intracytoplasmic vacuoles in both dendrites and neurons. Occasional neurons contain tubulo-fibrillar material. Wallerian-like degeneration may be present in ventral horn, intramedullary ventral root exit zone, and proximal ventral roots. Distal axons are atrophic.
- c. Chronic Disease - This form is characterized by slowly progressive disease, with dogs surviving well into adult life. Clinical signs are usually mild, except for overall thinness. One dog has reportedly survived for more than 7 years without marked motor involvement. Microscopically, motor neurons tend to be intact and only few axonal swellings are observed.

Electromyography reveals sporadic fibrillation potentials and positive sharp waves. Nerve conduction studies are normal. Degenerative changes in peripheral nerves result in neurogenic atrophy, particularly in more proximal appendicular and paraspinal muscles.

The pathogenesis of HCSMA remains unclear. The neurofilamentous swellings of proximal axons, atrophy of distal axons, and degeneration of motor neurons are believed to be associated with impaired axonal transport of the neurofilament triplet proteins and a maldistribution of phosphorylated neurofilaments [133]. Cyclin-dependent kinase 5, an enzyme that phosphorylates neurofilaments and regulates neurofilament dynamics, is markedly increased in young HCSMA homozygotes prior to the development of significant neurofilament pathology [136]. In the accelerated and intermediate phenotypes, there is a reduction in axonal size in ventral roots, primarily in large axons, and the frequency of small-caliber axons is increased; however, the density of fibers in motor nerves is increased, suggesting that the changes in axonal size in motor nerves are associated with both growth arrest and axonal atrophy [137]. Results of recent studies suggest that motor unit failure is due to failure of neuromuscular synaptic transmission that precedes nerve or muscle degeneration [231]. Immunocytochemical and morphometric studies on dogs with intermediate and chronic phenotypes indicate that HCSMA cholinergic motor neurons are smaller, with fewer neurons expressing choline acetyltransferase, compared with controls [138]. Acidic excitatory amino acids may also play a role in the pathogenesis. There are significant reductions in the levels of endogenous aspartate, glutamate, N-acetylaspartate (NAA), and the neuropeptide N-acetyl-aspartyl-glutamate (NAAG) in the spinal cord in homozygous but not heterozygous HCSMA [139]. In contrast, the activity of N-acetylated-alpha-linked-amino dipeptidase, an enzyme that cleaves NAAG into NAA and glutamate, is significantly increased. None of these parameters is affected in the motor cortex or occipital cortex. Other studies on colony dogs have revealed low serum vitamin E concentrations in affected dogs, especially puppies, but no mutations in a major cytosolic antioxidant enzyme, Cu/Zn superoxide dismutase (SOD1) [232,233].

Prognosis is favorable only for Brittany Spaniels with the chronic form of the disease. At this time, there is no treatment. A LMN disease associated with spinal muscular atrophy has been reported in young **Rottweiler puppies** [140-142]. Signs were seen at 4 weeks of age and included pelvic limb ataxia that rapidly progressed to tetraparesis and tetraplegia over the ensuing 2 to 4 weeks. Additionally, spinal reflexes were diminished or absent (except for flexor and perineal reflexes), and there was slight intention tremor, limb tremor after exercise, depressed postural reactions, megaesophagus with regurgitation, inability to hold up the head, generalized muscle atrophy, and development of pelvic limb extensor rigidity. Analysis of CSF was normal. Microscopic findings were characterized by central chromatolysis and swelling of many neurons in ventral horns of the spinal cord and in several brainstem nuclei, including red, oculomotor, trigeminal motor, and ambiguus nuclei. Wallerian-like degeneration was prominent in neuropil of spinal cord and in peripheral nerve. Affected neurons contained prominent Golgi complexes and numerous neurofilaments.

De Lahunta has described a young Rottweiler puppy with some clinical and pathological variations [1]. Tetraparesis was evident without significant muscle atrophy. The swollen chromatolytic motor neurons contained widely dispersed endoplasmic reticulum but few neurofilaments, and degenerative changes were found (in addition to those neuronal populations described in the Rottweilers above) in neurons of the spinal ganglia and various medullary sensory neurons, including vestibular, cochlear and cerebellar nuclei.

Neurofibrillary accumulation has also been reported in a 12 week old **Collie** puppy with signs of progressive neurological disease [143]. The puppy was weak, had difficulty rising from a sitting position, and would frequently collapse when walking. Patellar reflexes were diminished. Cranial nerve function appeared normal except for absence of menace response and presence of widely dilated and unresponsive pupils. A diffuse neuronal abnormality was observed microscopically. An intracytoplasmic slate-gray material that appeared fibrillar and often arranged in whorls distended the cell body and displaced the nucleus and Nissl substance peripherally. Lower motor neurons of the ventral gray column were affected in the first cervical spinal cord segment, as well as neurons in various brainstem nuclei, including vestibular nuclei, spinal nucleus of the trigeminal nerve, ventral nucleus of the trapezoid body, central tegmental nucleus, oculomotor nuclei, mesencephalic nucleus of the trigeminal nerve, a few neurons in the rostral colliculi, and many thalamic and hypothalamic neurons. A few Purkinje cells were affected as were occasional large pyramidal neuron in layer V of the cerebral cortex. Ultrastructurally, there was abnormal proliferation of 12-nm neurofilaments arranged in whorls and linear arrays.

There are only a few reports of **cats** with motor neuron disease. A LMN disease with accumulation of neurofilaments has been described in a 10 week old female, Domestic Shorthair cat with clinical signs of tetraparesis that progressed to tetraplegia within a few weeks [144]. There was diffuse atrophy of appendicular musculature. Spinal reflexes were absent. Mentation and cranial nerve function were normal. Abnormal spontaneous fibrillation potentials were detected in limb muscles with EMG. CSF analysis was normal. Microscopically, widespread degeneration was seen in the large motor neurons of the lateral parts of the ventral horns in the cervical and lumbar intumescences of the spinal cord. Nissl substance was missing in some cells, while nuclear destruction accompanied by advanced chromatolysis resulted in formation of ghost cells. Glial nodules were seen in areas of lost neurons. A diffuse argentophilia with indistinct whorls was seen after silver impregnation of the affected neurons. Wallerian degeneration was found in ventral spinal nerve roots and peripheral nerves of the affected spinal cord segments. No other lesions were found in the spinal cord, brainstem, cerebellum, or cerebrum. Ultrastructurally, the degeneration of nerve cells was characterized by abnormal proliferation of neurofilaments, which were also seen in dendritic spines but not in axons. The fibrillary material had a diameter of about 10-nm.

Summers and colleagues described a LMN disorder in 2 older cats with signs of crouched gait, severe muscle atrophy, and tongue fasciculations [10]. Signs were present in one cat for 3 years and for 1 year in the second cat. Profound loss of motor neurons in the ventral horns were observed in cervical, thoracic and lumbar cord segments, accompanied by mild astrocytosis and numerous macrophages in the ventral horns. Extensive loss of axons was noted in the ventral roots. While very few motor neurons were available for study, occasional swollen axons distended with filamentous accumulations were found in the ventral horns. In the brainstem, vacuolated neurons or occasional ghost cell were found in oculomotor and facial nuclei. The authors make the caveat that they were unsure if the cats had the same disorder or if the condition was inherited or acquired.

### **Multisystem Neuronal Abiotrophies**

Several familial neurodegenerative disorders occur in young dogs that are characterized by progressive degeneration and loss of neurons in multiple neuronal systems. These entities are considered to represent system degenerations and have been termed multisystem neuronal abiotrophies [1,10].

### **Multisystem Neuronal Abiotrophy in Swedish Lapland Dogs**

An autosomal recessive neurodegenerative disease has been reported in Swedish Lapland dogs [145] that has been compared to infantile spinal muscular atrophy (Werdnig-Hoffman disease) [124]. Signs appear in affected puppies at 5 to 7 weeks of age. The onset is marked by thoracic or pelvic limb weakness that progresses rapidly to tetraparesis and tetraplegia. In 7 to 14

days after onset, puppies are in sternal recumbency and unable to stand. The carpi become fixed in a flexed position and pelvic limbs become extended with extreme flexion of the stifles. Subsequent muscle wasting and deformity are most pronounced in distal portions of the limbs. Spinal reflexes are reduced or absent, and electromyographic examination reveals denervation potentials. Microscopically, central and peripheral neuronal chromatolysis along with neuronal degeneration and loss are observed in the lateral parts of the ventral horns in cervical and lumbar intumescences, and in dorsal root ganglia. While no degenerative changes are found in any of the motor nuclei of the brainstem, other affected neurons include those in the dorsal gray column of the spinal cord, trigeminal ganglia, and the trigeminal mesencephalic nucleus. Degeneration of Purkinje cells is pronounced and associated with chromatolysis and ischemic cell change, with prominent axonal degeneration in the cerebellar foliate white matter and cerebellar roof nuclei. The neuronal changes are accompanied by diffuse axonal degeneration in the dorsal roots, dorsal funiculus of the spinal cord, and spinocerebellar tracts, as well as in the trigeminal, optic, and vestibulocochlear nerves. It is suggested that the pathologic process is initially manifest as degeneration in the terminal portion of the axon and then proceeds toward the cell body as a "dying back" phenomenon. Prognosis is poor and there is no treatment.

### **Multisystem Neuronal Abiotrophy in Cocker Spaniels**

This is a slowly progressive neurological disease that has been reported in 4 red-haired Cocker Spaniels (1 female and 3 males), aged between 10 and 14 months [146]. The dogs had a common male ancestor. Clinical signs began in all dogs several months before presentation and included behavioral changes such as apathy, loss of house training, loss of recognition of persons and objects, hyperactivity, hypersexuality, and aggression. All dogs appeared excessively anxious and were easily startled. Menace response was absent in all dogs. One dog had a slight head tilt, and another had fixed miotic pupils. Hypermetria, intention tremors, ataxia, and wide-based stance were noted in three dogs. Other variable signs included periodic falling, bumping into objects, pacing, and circling. Delayed knuckling reactions occurred in one dog. Spinal reflexes were normal. CSF analysis and skull radiography were unremarkable. Pathological findings included bilaterally symmetrical lesions in gray and white matter. There was diffuse nerve cell loss, gliosis, and occasional dystrophic axons throughout subcortical and brainstem nuclei, including septal nuclei, globus pallidus, subthalamic nuclei, substantia nigra, tectum, medial geniculate bodies, and cerebellar and vestibular nuclei. White matter changes, which were considered to be secondary to the neuronal loss, included gliosis, moderate numbers of axonal spheroids, perivascular macrophages, and myelin loss. The white matter changes were most pronounced in central cerebellar areas, corpus callosum, thalamic striae, subcortical white matter, and in fimbriae of the fornix. No lesions were noted in the one spinal cord examined.

The etiopathogenesis of this unique condition is presently unknown. Pedigree studies suggest a possible autosomal recessive mode of inheritance. Prognosis appears to be poor. Corticosteroid therapy in two dogs was ineffective.

### **Multisystem Neuronal Abiotrophy in Cairn Terriers**

This neurodegenerative condition in young Cairn Terriers of either sex has been termed "progressive neuronopathy" [147] and "multisystemic chromatolytic neuronal degeneration" [148]. It has been seen in the USA, Australia, Holland, and the UK [148-150]. Clinical signs begin around 5 months of age and are characterized by pelvic limb weakness that progresses to tetraparesis, depressed spinal reflexes and diminished proprioception, incoordination, hypermetria, and head tremor.

Microscopic findings include central and/or peripheral chromatolysis in medial aspects of dorsal and ventral horns (including Clarke's column) of the spinal cord as well as various brainstem nuclear groups-cuneate nucleus, glossopharyngeal and vagus nuclei, lateral vestibular nucleus, reticular nuclei of the medulla, cerebellar roof nuclei, red nucleus, and mesencephalic nucleus of the trigeminal nerve. Typically, neuronal loss is not a feature of this disorder. Moderate white matter changes (including axonal degeneration and considered to be secondary to the neuronal changes) are seen in lateral and ventral columns of the spinal cord, brainstem, dorsal and ventral nerve roots, and in peripheral nerves.

A range of clinical and pathological variations may occur in this condition. In one report of a 4 month old female Cairn Terrier with mild episodic paraparesis, clinical signs were apparent at 4 months of age and were confined to the pelvic limbs [148]. In addition, chromatolytic degeneration of varying pattern (e.g., central, peripheral, or patchy) was observed in neurons of the cerebral cortex, in spinal, autonomic and myenteric ganglia, as well as in brainstem and spinal cord neuronal populations mentioned above. In another case report involving an 11 week old Cairn Terrier [151], pelvic limb weakness was noted initially. Signs rapidly progressed to include head tremors, inability to stand, uncoordinated movements involving the head, trunk and limbs, positional nystagmus, absent patellar reflexes, and absent menace response. Muscle atrophy was not evident. This dog also manifested episodic cataplectic attacks, characterized by generalized hypotonia or atonia that were responsive to imipramine (see narcolepsy). In this dog, a symmetrical thoracolumbar myelomalacia was found in dorsal horns and adjacent funicular white matter. Ultrastructural studies in these two case reports revealed dispersion and loss of ribosomes in chromatolytic neurons, often accompanied by numerous mitochondria [148,151]. More recently, the condition has been reported in two older Cairn Terrier littermates, an 18 months old male and an 11 month old female [150]. The initial clinical signs were characterized by hind limb weakness and ataxia, which deteriorated with exercise. These signs progressed



over several months to tetraparesis.

### **Multisystem Neuronal Abiotrophy in Miniature Poodles**

This degenerative condition has been described in two male puppies from a litter of three [152]. Clinical signs appear at 3 to 4 weeks of age and were characterized by rolling from side to side, inability to stand or right into sternal position, periodic opisthotonus, intention tremors involving head and sometimes, trunk and limbs, and absent menace response. Abnormal vertical nystagmus could be elicited. Microscopically, degeneration was present in the cerebral cortex and cerebellum. Cerebellar cortical atrophy was characterized by extreme loss and degeneration of Purkinje cells which appeared either pale, swollen and vacuolated or shrunken and hyperchromatic associated with eosinophilia and nuclear pyknosis [2]. In addition, there was granule cell loss, gliosis in the molecular layer, and axonal degeneration in foliate white matter. Vacuolar degeneration was present in the lateral (dentate) cerebellar nuclei. Diffuse degenerative (hyperchromatic) and vacuolar changes were also present in neurons throughout the cerebral cortex. Ultrastructural studies indicate that vacuolar neuronal degeneration was associated with marked dilation of endoplasmic reticulum and loss of ribosomes. Shrunken Purkinje cells had decreased numbers of Nissl bodies and there were accumulations of mitochondria and lamellar bodies. The latter, stacked derivatives of endoplasmic reticulum, were not seen in shrunken cerebral perikarya. Lamellar bodies reached giant proportions in the dendritic stems of degenerating Purkinje neurons. In Purkinje axons, however, honeycombed aggregates of axoplasmic tubules usually predominated. The cytological changes in these Poodle pups were notably different from those reported in ultrastructural studies of canine inherited cerebellar degenerations. The genetic status of this condition remains to be confirmed.

### **Nervous System Degeneration in Ibizan Hounds**

A neurodegenerative condition has been described in Ibizan Hounds characterized by a gait abnormality that occurs around the time puppies first begin to walk [10]. Puppies manifest an ataxic-dysmetric gait that affects the hind limbs initially and then progresses to the forelimbs. The gait has a bouncy, dancing character associated with awkward strides, truncal swaying, and frequent falling. Patellar reflexes are absent, but without evidence of muscle atrophy. No gross lesions are seen in the CNS. Microscopic changes include bilaterally symmetrical degeneration of ascending and descending white matter tracts throughout all levels of the spinal cord and involving all funiculi. Changes appear more severe in the thoracic cord, and especially involve the lateral areas of the dorsal funiculus, the superficial and dorsal portion of the lateral funiculus, and superficial regions of the ventral funiculus. Numerous large spheroids are found in the cochlear neurons of the trapezoid body. The dorsal nucleus of the trapezoid body appears gliotic. Degenerative changes, including myelin and axonal degeneration and macrophage infiltration are seen in spinal roots, especially ventral roots, and in peripheral nerves. An autosomal recessive mode of inheritance is suggested by pedigree analysis. The condition is considered to have clinical and pathological similarities to hereditary ataxia in Smooth-haired Fox Terriers and Jack Russell Terriers.

### **Neuroaxonal Dystrophy**

Neuroaxonal dystrophy (NAD) is a degenerative neurological disease that has been reported in cats and dogs. NAD is transmitted as an autosomal recessive trait in Tri-Colored cats and is familial or believed to be inherited in a similar fashion in dogs. The disease is characterized by membrane-filled swellings ("spheroids") of preterminal regions of axons and in synaptic terminals within the CNS [10]. The pathogenic mechanisms underlying the development of this type of axonal abnormality are not well understood, although it is believed that the degeneration starts in the distal axon and progresses proximally, resulting in eventual death of the neuronal cell body [153]. Neuroaxonal dystrophies are considered further examples of abiotrophic processes in animals [1]. In humans, NAD can be separated into 3 types [153]:

- a. physiological NAD: a normal part of brain aging;
- b. primary NAD: diseases in which the main pathology is neuroaxonal dystrophy; and
- c. secondary NAD, occurring as a "reactive" process in another condition.

A similar morphological classification seems to exist in animals. In general, clinical signs of cerebellar-like disease develop in young animals with primary NAD and signs are typically progressive. Ancillary laboratory tests, such as CSF analysis and electrodiagnostics are usually normal. There is no treatment. Prognosis is guarded due to the progressive nature of the disease.

### **Neuroaxonal Dystrophy in Rottweilers**

A recessive mode of inheritance is suspected in Rottweiler dogs with NAD [154-156]. Clinical signs are characterized by slowly progressive ataxia, hypermetria, and wide-based stance beginning in the first year of life, and in some cases, as early

as 10 weeks of age [157], although in one report, 3 dogs were normal in the first year of life, while a fourth dog only showed poor coordination and clumsiness during the first year [158]. Some dogs stand with legs crossed or on three legs with one elevated. Mild proprioceptive deficits have been reported [157]. As the neurological deficit progresses, sometimes over several years [155], head intention tremors, postural and spontaneous nystagmus (positional and then continuous), and menace deficit with preservation of vision and pupillary light reflexes, may be noted. In advanced cases, dogs are unable to climb or ascend stairs. Some Rottweilers have been observed with the disorder for more than 6 years. Muscle bulk, tone and strength appear to be preserved [154]. Hematology and blood chemistries are normal, as are plasma and urine amino acid levels and serum vitamin E levels. Analysis of CSF is usually normal, although a mild protein increase has been reported in one affected dog [158]. Nerve conduction studies are normal, while EMG studies may reveal the presence of fibrillation potentials and positive sharp waves in interosseous muscles [154,158].

Histological changes are progressive and tend to mirror the clinical signs [10]. Grossly, the cerebellum is normal or mildly atrophic [158]. Microscopic studies reveal the presence of massive numbers of axonal spheroids in gray matter of many regions of the neuraxis, especially in sensory axon terminals, e.g., the dorsal horn of the spinal cord, nuclei gracilis and cuneatus, accessory cuneate nucleus, sensory nucleus of the trigeminal nerve, nucleus of the dorsal spinocerebellar tract, granular layer of the cerebellum, vestibular nucleus, and lateral and medial geniculate bodies. The spheroids (up to 100  $\mu$ m in diameter) are often eosinophilic and either smooth or granular. Some may be palely vacuolated with central cores of swirling filaments or granules that are often argyrophilic. The central cores may stain with Luxol fast blue and periodic acid-Schiff. Some spheroids retain portions of the myelin sheath, while in others, the sheath is attenuated and frequently absent. In some dogs, a marked loss of cerebellar Purkinje cells has been reported, especially in the vermal lobules and floccules [154]. Ultrastructurally, spheroids are filled with accumulations of smooth membrane-bound vesicles, membranous lamellae, dense bodies, tubulovesicular arrays, and neurofilaments [158]. The pathogenesis of this condition remains uncertain, although perturbations of axonal transport have been suggested [158], a theory supported by findings of accumulated synaptic proteins (including synaptophysin, synapsin-I, synaptosomal-associated protein of 25 kDa (SNAP-25), Rab 3a, and alpha-synuclein) in dystrophic axons [235]. Prognosis is poor because of the slow progression of the disease although affected dogs may be acceptable pets for a long time.

An unusual case of neuroaxonal dystrophy has been described in Australia in a 15 week old female Rottweiler puppy presenting with an acute onset of coughing and severe inspiratory stridor [159]. The dog was surgically treated for vocal cord paralysis. A few weeks post-surgery, the dog developed a bunny-hopping hind limb gait when running. Soon after, the owners reported that the dog collapsed while exercising and at rest. On reexamination, the dog had a severe inspiratory dyspnea, pronounced inspiratory stridor, was cyanotic and weak. Proprioceptive deficits developed soon after. Microscopic findings included vacuolation, hemorrhage, and chromatolysis of neurons in the medial vestibular nuclei. Additionally, there was vacuolation of the inferior cerebellar peduncle, and vacuolation and axonal swelling with macrophage infiltration in the spinothalamic tract at the same level. In the midbrain, there was vacuolation of the corticospinal tracts, the medial longitudinal fasciculus and gliosis of the rostral colliculus. Gliosis and neuronal vacuolation was found in the nodular lobule of the cerebellar vermis and inferior olivary nucleus. In the spinal cord, axonal swelling and vacuolation were present in various white matter tracts, including the ventral and dorsal spinocerebellar pathways, the fasciculus cuneatus, and the ventral corticospinal tract. Focal hemorrhages were present in the gray columns. This atypical neuroaxonal dystrophic condition has clinical and histopathological similarities to progressive tetraparesis and laryngeal paralysis in young Rottweilers with neuronal vacuolation and axonal degeneration [160] (see spongy degeneration in gray matter).

### **Neuroaxonal Dystrophy in Collie Sheep Dogs**

A cerebellar neuroaxonal dystrophy in Collie Sheep dogs has been reported in New Zealand and Australia [161]. Clinical signs developed from 2 to 4 months of age and gradually increased in severity. Signs included hypermetria, wide-based stance, difficulty in maintaining balance, intention tremor, and ataxia. Body growth, learning ability and social behavior with other dogs were normal. Microscopically, numerous spheroids, appearing as round or oval eosinophilic and moderately argyrophilic bodies ranging from 4 to 36  $\mu$ m in diameter, were found in cerebellar roof nuclei and lateral vestibular nuclei, and in the central cerebellar, adjacent peduncular, and folia white matter, where they were associated with mild Wallerian degeneration. Purkinje cells were normal. Spheroids were also seen in molecular layer of the cerebellum, nucleus gracilis, substantia nigra nuclei, rostral colliculus, cerebral cortex, and gray matter of the spinal cord. The spheroids were accompanied by moderate diffuse gliosis. The history of several affected puppies in litters from successive mating of the same sire and dam suggested an autosomal recessive mode of inheritance.

### **Neuroaxonal Dystrophy in Chihuahuas**

A degenerative neuroaxonal dystrophy has been reported in 2 female Chihuahua littermates [162]. At 7 weeks of age, there was sudden onset of tremor and exaggerated gait. Grossly, a moderate dilatation of the lateral ventricles was noted. The main histopathological change was presence of spheroids throughout the white matter of the brain and were especially prominent

in internal capsule, cerebellum, lateral geniculate body, anterodorsal nucleus of the thalamus, acoustic tubercle, superior and inferior olives, and corticospinal and spinothalamic tracts. Spheroids were also present in the lateral cuneate nucleus, and gray matter of the thalamus, but infrequently in the cerebral cortex. Minimal changes were found in the spinal cord. Ultrastructurally, the major accumulated organelle was a membrane-bound body with containing numerous mitochondria and dense bodies. In the gray matter many of the spheroids had synaptic clefts indicating that in these sites the spheroids were presynaptic.

### **Neuroaxonal Dystrophy in Papillons**

Neuroaxonal dystrophy has been reported in a litter of five 14 week old Papillon puppies [163]. Clinical examination revealed signs of ataxia, hypermetria and depressed postural reflexes affecting all four limbs. The severity of these signs varied between members of the litter. The condition became progressively worse and by 19 weeks of age all but the least severely affected pup (the single male of the litter) had deteriorated to the point that euthanasia was indicated on humane grounds. Pathological examination revealed widespread changes in both white and gray matter of the neuraxis caudal to the forebrain, particularly involving the dorsolateral white matter of the spinal cord, characterized by axonal swellings typical of neuroaxonal dystrophy.

### **Neuroaxonal Dystrophy in a Jack Russell Terrier**

A 9 week old Jack Russell terrier with progressive ataxia had histopathological lesions consistent with neuroaxonal dystrophy [164]. Gross observation revealed absence of the septum pellucidum, hypoplasia of the corpus callosum and marked bilateral hydrocephalus. Light microscopy of the CNS showed extensive axonal swellings principally in the gray matter of the brainstem where the sensory nuclei were most affected, especially medullary proprioceptive and vestibular nuclei, and in diencephalic nuclei [2]. Spheroids were also seen throughout the spinal cord gray matter with a few also present in the dorsal funiculi. Ultrastructurally, spheroids were identified as axonal terminals and dystrophic boutons and characterized by accumulations of membrane bound bodies. Clinical and morphological findings were similar to those identified in human infantile neuroaxonal dystrophy (Seitelberger's disease).

### **Feline Neuroaxonal Dystrophy**

Neuroaxonal dystrophy has been reported in Domestic Tri-Colored cats as an autosomal recessive condition [165] and has been termed feline hereditary neuroaxonal dystrophy (FHND). Clinical signs occurred in kittens around 5 - 6 weeks of age, at which time head tremors and head shaking were observed. Signs progressed to marked incoordination of gait and hypermetria. Affected kittens had a lilac color that darkened with age. Unaffected littermates were black. There was gross atrophy of the cerebellar vermis. Microscopically, axonal spheroids were found principally in the inferior olivary nucleus and lateral cuneate nucleus. Spheroids were noted also in the brainstem tegmentum, nucleus ventralis and ventralis anterior of the thalamus, and the cerebellar vermis. The spheroids had a finely granular homogenous quality, sometimes with a periodic acid-Schiff-positive central dark core. The spheroids were seen with and without ballooned cell processes. The latter type was found in the previously mentioned areas but also in medial lemniscus, medial longitudinal fasciculus, region of the central tegmental tract, and in dorsal roots of the spinal cord. These changes were accompanied by loss of neurons, including Purkinje and granule cells of the cerebellar vermis, and glial proliferation that was prominent in the molecular layers of the cerebellar vermis. Spheroids were present in the spiral ganglia of the inner ear, along with neuronal depletion.

Ultrastructurally, most spheroids had a myelin sheath. Spheroidal morphology was variable and included large membrane-bound vacuoles with a homogeneous electron-opaque interior, numerous small mitochondria and osmiophilic dense bodies, sometimes within membrane-bound vesicles, and variable neurofilaments that were often separated by multilaminated membranous structures.

Neuroaxonal dystrophy (multifocal swollen axons in brainstem, medulla, and spinal cord; swollen myelin sheaths in spinal cord) with cerebellar abiotrophy (characterized by multifocal Purkinje cell loss and displacement of remaining Purkinje cells into the granular layer of the cerebellum with molecular layer gliosis) has recently been reported in 2 littermate Domestic Shorthair cats with dilute gray coat color [218]. Progressive cerebellar signs, stunted growth, muscle atrophy, and apparent blindness (absent menace response, miotic pupils and unusual green irises) began a few weeks after birth.

A syndrome resembling (FHND) has been studied in siblings from several litters of Domestic Shorthair cats born to the same queen [166]. The disorder was characterized by a sudden onset of hind limb ataxia, from 6 to 9 months of age, that slowly progressed to hind limb paresis with crouched standing or dragging-rolling gait, and eventual paralysis. Hematology, biochemistries, urinalysis, and electrodiagnostic testing were normal. Histologically, there was marked ballooning of axonal processes, with spheroid formation and vacuolation in specific regions of the brain and spinal cord. Some dystrophic axons contained a central periodic acid- Schiff positive core. Neuronal loss and gliosis were seen in certain brainstem nuclei (most severe in the lateral and medial cuneate nuclei and nucleus gracilis), the thoracic nucleus (dorsal nucleus or Clarke's column)

in the gray matter of the spinal cord, and the cerebellum (especially in the cerebellar nuclei and granular layer of the cerebellar vermis, with associated degeneration and loss of Purkinje cells). Degenerative changes in white matter were seen in ascending and descending tracts of the spinal cord and were most severe in the fasciculus gracilis in the cervical cord. The spheroids ranged in size from 25 to 100  $\mu\text{m}$  with similar microscopic and ultrastructural features to those described above in FHND. The syndrome in this report differed from FHND in Domestic Tri-Colored cats in that no inner ear involvement was seen, onset of clinical signs occurred at a later age, and there was involvement of cerebellar nuclei and spinal cord. In addition, although some of the affected cats did have diluted coat colors, abnormal coat color was not always associated with clinical disease.

Neuroaxonal dystrophy has also been reported in two 5 week old (male and female) Siamese kittens with progressive neurological signs including head tremor, hypermetria, proprioceptive deficits (all limbs), hind leg ataxia and paralysis. Signs were initially noted at 2 weeks of age [167]. The kittens had heightened responsiveness to touch and noise. Coat color in the kittens was normal. Grossly, the cerebellum was slightly smaller than normal in both cats. Microscopically, the most prominent changes were found in the brainstem and characterized by ballooning of cell processes, axonal spheroids, and neuronal depletion, principally in the lateral cuneate nucleus. Many spheroids had a dense, central eosinophilic core. Degeneration and loss of Purkinje cells were also observed, especially in the cerebellar vermis. In addition, vacuolation was seen locally around Purkinje cells and in the granular layer, as well as in the white matter of the cerebellum and spinal cord. The condition was believed to be hereditary.

### **Rottweiler Leukoencephalomyelopathy**

This neurodegenerative disorder has been recognized in the USA, Netherlands, UK, and Australia affecting young Rottweiler dogs of either sex from about 1.5 to 4 years of age [168-171]. The etiopathogenesis is unknown, although the disease is considered to be inherited and transmitted as an autosomal recessive trait [171]. Clinical signs include ataxia, tetraparesis, hypermetria, proprioceptive loss, and normal or exaggerated spinal reflexes with increased muscle tone. Signs are often first seen in thoracic limbs [169-171]. The disease progresses over a 6 to 12 month period to the point where animals have difficulty in rising and standing, and there is frequent stumbling, scuffing of the paws, and falling [170]. There is no muscle atrophy, extensor tone is often increased, and pain sensation may be decreased [171]. Cranial nerves, vision, pupillary reflexes, and menace responses are unaffected. All diagnostic studies including hematology, blood chemistries, CSF analysis, electrodiagnostics (EMG and NCVs), plain radiography, and myelography are normal.

Bilateral, symmetrical lesions may be seen throughout the spinal cord, but are most severe in dorsal and lateral funiculi of the cervical cord segments. In transverse sections of fixed specimens, these lesions appear grossly as areas of increased pallor and opacity. In the brainstem, lesions tend to be bilaterally symmetrical and may be found in the spinal tracts of the trigeminal nerve, caudal cerebellar peduncles, deep cerebellar white matter, subventricular rostral medullary tracts, pyramidal tracts, and the medial lemniscus. Optic nerves and tracts may also be affected (but not to the point of causing visual deficits) [171]. Occasionally, diffuse or patchy lesions occur in the corona radiata [171]. Cranial nerves and autonomic ganglia are normal. Histopathological changes include rarefaction and polymicrocavitation of the white matter associated with demyelination, edema, diminished myelin staining, dissociation of myelin sheaths, gemistocytic astrocytosis, fibrillary gliosis, and macrophage infiltration [170]. In the severe cervical cord lesions, a narrow rim of normal white matter is seen between the edge of the lesion and the pial surface [169]. Wallerian degeneration is not a feature of this condition [171], and therefore, not surprisingly, axonal degeneration is mild, although a few swollen degenerating axons are seen occasionally. There is minimal inflammation or endothelial cell proliferation. Axonal spheroids are variably present, but in one dog, these structures were found in accessory cuneate nucleus, nucleus gracilis, nucleus cuneatus, and the nucleus of the dorsospinocerebellar tract, but were not associated with neuronal loss [169]. Ultrastructurally, myelin splitting, thinly myelinated axons and naked axon sheaths separated by broad astroglial processes, are seen [169,170]. There is little evidence of axonal swelling or neurofilament aggregation. Slocombe and colleagues found evidence of scattered swollen and vacuolated nerve sheaths within hind limb peripheral nerves in all of their affected dogs [170].

Possible storage disease has been ruled out in affected Rottweilers by the demonstration of a battery of normal lysosomal enzyme activities in peripheral blood leukocytes [170]. Presently, there is no treatment. Prognosis is poor.

This condition needs to be differentiated from neuroaxonal dystrophy in Rottweilers, which is often seen before 1 year of age, and is slowly progressive over several years. Clinical signs include hypermetria, head tremors, and nystagmus, but typically, there is no paresis [155,171]. Young adult Rottweilers (18 to 20 months of age) with cervical spondylomyelopathy and signs of progressive proprioceptive loss and ataxia may also be confused clinically with Rottweiler leukoencephalomyelopathy [168].

### **Spongy Degeneration of the CNS**

Spongy degeneration of the CNS in children has been termed Canavan's syndrome (van Bogaert-Bertrand type of spongy degeneration) and is characterized by accumulation of vacuoles in a variety of cells, particularly astrocytes [4], which also

contain abnormally structured elongated mitochondria [172]. The vacuoles result from excessive fluid accumulation, seemingly from metabolic disturbances that produce dysmyelination. Studies suggest biochemical heterogeneity in the pathogenesis of infantile spongy degeneration, including deficient activity of aspartoacylase (antemortem diagnosis can be made using cultured fibroblasts) and astrocytic mitochondria with reduced levels of adenosine triphosphate [4,173,174]. Increased amounts of N-acetylaspatic acid are found in urine and plasma [175]. In this condition, demyelination can be prominent but axons and oligodendroglia are not extensively affected [4]. Familial and hereditary forms of spongy degeneration have been recognized sporadically in young dogs and cats and the changes may be predominant in either white or gray matter.

### **Spongy Degeneration in White Matter**

Spongy degeneration has been observed in 2 young female **Labrador Retriever** littermates [176]. Clinical signs were noted between 4 and 6 months of age and were characterized by progressive ataxia-dysmetria of head, trunk, and limbs, wide-based stance, hyperreflexia with clonus, muscle atrophy, and episodes of exaggerated rigidity and opisthotonus. Excitement increased the frequency of the episodes. In one dog, signs included periodic extension of the forelimbs, dorsiflexion of the head, and falling over backwards. In the second dog, one spell of marked extensor rigidity and opisthotonus lasted for 2 hours. Cranial nerve function (apart from possible auditory deficits in one dog and a visual placing deficit in the second dog) and proprioception appeared normal, and dogs retained bowel and bladder control. At 11 months of age, one dog became very weak and dysmetric and all muscle groups were atrophic. This dog could take no more than 2 or 3 steps without falling or collapsing. Routine hematology, blood chemistries, urinalysis and CSF tests were all within normal limits. Distal tibial nerve conduction velocities were considered slow in the 11 month old dog and EEG studies revealed normal background activity with occasional spiking in the left frontal region. Microscopically, spongy degeneration of the white matter of the CNS and PNS was found, with most prominent lesions in cerebellar peduncles, deep cerebellar white matter, and in the subcortical and deep white matter of all lobes of the cerebrum [177]. Similar lesions were found in the tracts of some cranial nerves, in the thalamic area, midbrain and brainstem, and in the white matter of the spinal cord. These areas were associated with hypertrophied cell bodies, processes, and perivascular footplates of fibrous astrocytes. Myelin loss was described, but axons were normal and there was no evidence of myelin breakdown or inflammation. Ultrastructural studies indicated that the vacuolation was caused by myelin separation at intraperiod lines between major dense lines. The hypertrophic astrocytes had dilated cytocavitary systems, membrane-bound crystalline inclusions, abundant intermediate filaments, and degenerated mitochondria. The clinical, histological, and ultrastructural findings resembled those reported for the juvenile form of Canavan's disease (van Bogaert and Bertrand type) in children. The cause of this condition remains uncertain, but a biochemical lesion involving a membrane-associated adenosine triphosphatase ion transport system in astrocytes has been proposed [177]. Prognosis of dogs with this disorder appears to be poor. Treatment with acepromazine (0.25 mg/kg, IM) decreased the frequency of the episodes of extensor rigidity but resulted in marked weakness. Diazepam (15 mg, IV) did not improve the extensor rigidity-opisthotonus.

A progressive neurological disorder has been reported recently in several related litters of **Shetland Sheepdogs** [178]. Clinical signs, beginning at 7 days to 3 weeks of age, included seizures with increasingly frequency and severity, mental depression, inability to assume sternal recumbency from a lateral position, whole body hyperesthesia, intention tremors of head and neck, inability to ambulate, extensor and flexor rigidity and spasticity of all 4 limbs. Patellar and sciatic reflexes were hypertonic. Affected puppies tended to remain in an opisthotonic position at rest. Serum biochemistry profile, hematology, urinalysis, and CSF studies were normal. CT scans revealed diffuse hypomyelination of white matter in one affected pup, along with dilation of the lateral and 4th ventricles. Electrodiagnostic studies (EMG and NCVs) were normal. In puppies euthanized, no gross lesions were noted. Microscopic studies revealed severe, diffuse, patchy vacuolation of the white matter of the brain and spinal cord that did not appear to worsen with age. Spongiosis was most severe in the cerebellar medulla and folial white matter and the corona radiata. Vacuolation was moderate and patchy in the cerebral white matter and mild in the optic tracts and brainstem, although the caudal colliculi and ventrolateral pons were often involved. The corpus callosum was minimally affected. In the spinal cord, all white matter tracts were affected, especially those in the dorsal funiculi. The CNS vacuolation was not accompanied by glial cell response and there was no evidence of swollen, degenerating axons or axonal debris. In a few puppies, cerebellar Purkinje cells had subtle changes including intracytoplasmic vacuolation, swollen dendrites and axons, and some cells appeared to be undergoing degeneration. Ultrastructurally, the vacuoles were associated with interlamellar splitting of myelin sheaths. Cytoplasmic vacuolation of Purkinje cells corresponded to dilation of the endoplasmic reticulum. Vacuolation was seen occasionally in nerve roots, although peripheral nerves were normal. The disorder was compared to Canavan's disease, although diminished aspartocyclase enzyme activity in tissue or N-acetylaspatic aciduria was not found. In addition, biochemical screening for known human organic acid or aminoacid abnormalities (such as maple syrup urine disease, phenylketonuria, hyperglycinuria, and homocysteinuria) were negative. The mode of inheritance of this familial condition was not determined, although the authors considered an autosomal recessive inheritance unlikely due to the large number of puppies affected.

Spongy degeneration has also been described in **Samoyed** puppies [179]. Pelvic limb tremors were observed at 12 days of age, progressing to generalized tremors over the next 5 days. Microscopically, a generalized vacuolation of white matter was seen throughout the CNS. Changes were most severe in the cerebellum and spinal cord, and less severe in the cerebrum. No degenerative or inflammatory changes were found and dorsal and ventral spinal nerve roots were normal. There was no evidence of myelin breakdown. Axons appeared normal. Ultrastructurally, vacuolations arose from splitting and distension of the myelin sheaths, usually as a "blowout" to one side of the axon rather than encircling them. There was no evidence of astrocytic change or of expanded extracellular space. The cause was not determined.

A degenerative spongiform disorder has been reported in 3 **Silky Terrier** puppies from a litter of five [180]. Clinical signs were noted at birth and consisted of head nodding, approximately twice per second, and uncontrolled intermittent contractures of the vertebral column, especially muscles of the thoracolumbar region, at intervals of approximately 2 per second. Occasionally the pelvic limbs were lifted off the ground during these contractures. The episodes were intensified with excitement and decreased markedly after a period of enclosure in a confined space. Low intensity contractions continued during sleep. Signs did not appear to be progressive. A spongy state, along with pallor of myelin staining, was found throughout the cerebral white matter, especially in the corpus callosum, optic tracts, and subcortical cerebral and cerebellar white matter. A large number of Alzheimer type II protoplasmic astrocytes were found in severely affected areas. Axons were normal.

Spongy degeneration has been reported in two female littermate kittens of the **Egyptian Mau** breed of cat (a small breed derived from the Siamese cat) [181]. Clinical signs, first noticed in kittens at 7 weeks of age, were characterized by pelvic limb ataxia and hypermetria. At 4 months of age, signs included a fixed, vacant stare, slow deliberate movements, and intermittent periods of severe depression and reduced activity, with frequent flicking movements of distal pelvic limbs when at full flexion. Blink, righting, and withdrawal reflexes were severely reduced. The condition improved with age in one kitten, although occasional episodes occurred. At 20 months of age, this cat was well grown, could jump and run, but had slight residual posterior ataxia. Another littermate (a male) was reported with hind limb ataxia that was first noticed by the owner at 10 months of age. Microscopically, there was widespread vacuolation throughout the brain and spinal cord. The intensity of this vacuolation varied, but was most severe in cerebral subcortical and sub-ependymal white matter, cerebellar foliar white matter, and the midbrain and brainstem. No neuronal abnormalities were seen and axons appeared to be unaffected. A paucity of myelin occurred in the vacuolar areas. Cerebrocortical and spinal cord gray matter also contained vacuoles, but were much less severely affected than the white matter. Ultrastructural studies revealed intramyelinic vacuolation, resulting from splitting of the intra-period line of the myelin lamellae. There was no evidence of myelin breakdown, and no neuronal, axonal, or glial changes, although a few small myelin figures were noted in the cytoplasm of astrocytic foot processes.

### **Spongy Degeneration in Gray Matter**

There are several forms of spongy degeneration characterized by their predominant involvement of gray matter. One of these, believed to be an autosomal recessive disease, occurs in **Bull Mastiff** puppies [182,190], of either sex, usually between 6 and 9 weeks of age, although in one affected dog, signs were initially noted at 7 months of age [182]. Clinical signs included ataxia, most obvious in pelvic limbs, hypermetria, proprioceptive deficits, and head tremor that was accentuated as animals attempted to eat. To date, all affected animals have had visual deficits and slowed menace reflexes. Less constant signs included hysterical behavior, compulsive forward movements, backing compulsively when called, lifting a fore limb while eating, circling, and an intermittent nystagmus (seen in the oldest dog). Some dogs appeared dull, disinterested in their surroundings, and difficult to train. Ancillary aids such as hematology, blood biochemistry and CSF analysis were within normal limits. Ventriculography revealed enlarged lateral ventricles, but unassociated with obstruction of CSF flow since the contrast passed from lateral ventricles to fourth ventricles and into the spinal subarachnoid space without hindrance. There was no evidence of megaesophagus and esophageal motility was normal. Magnetic resonance imaging in one report demonstrated symmetric hydrocephalus and two focal areas of increased signal intensity within the central nuclei of the cerebellum [190]. Macroscopic findings were characterized by moderate to severe communicating hydrocephalus with dilatation of all ventricles and the cerebral aqueduct. In addition, a yellow-brown discoloration of the cerebellar nuclei was seen. Microscopically, bilaterally symmetrical spongy lesions occurred in the three deep cerebellar nuclei (dentate, interpositus, and fastigial), where the lesions were most severe, in the lateral vestibular nucleus, and at the base of the inferior colliculus. The cerebellar lesions consisted of vacuolation, gliosis (increase in both microglia and astrocytes, many of which were hypertrophic), and frequent axonal spheroids. The neurons appeared normal but were often in close proximity to vacuoles and spheroids. No cerebellar cortical atrophy was observed despite the presence of occasional torpedoes in the granule cell layer. Many of the vacuoles were surrounded (partially or completely) by attenuated myelin. The vacuoles often contained myelin remnants and occasional axons. Degenerating axons were found within affected nuclei, the white matter of cerebellar folia, and the granule cell layer. Some swollen axons contained increased numbers of axoplasmic organelles, while others had dark, granular axoplasm. It was also reported that oligodendrocytes were degenerating. The basis for this vacuolar

change remains unclear. Prognosis is guarded. There is no treatment.

A similar spongiform disorder has been seen in young **Saluki** dogs with signs of seizures and behavioral changes, sleeping deeply, disinterest in their surroundings, aimless running, circling and back flips [2,183]. Skull radiography and CSF analysis were normal. EEG showed generalized low voltage activity in all leads. Microscopically, a pronounced spongiosis was present diffusely in the cerebrum (involving the deep laminae), brainstem and cerebellum. The spongiosis predominated in the gray matter, being especially severe in neuropil of olivary and cerebellar nuclei [2], but was also found in the thalamus, ventral internal capsule, tegmentum of the pons, nuclear areas of the medulla and optic nerve, usually accompanied by marked astrocytosis [183]. The lesions extended into white matter in some areas, such as at the junction of the lentiform nucleus with the internal capsule [2]. Lesions were not found in the spinal cord. A mild spongiform degeneration was noted in two clinically normal puppies. The condition was considered to be recessively inherited with variable expression.

Familial spongy degeneration has recently been reported in three **Cocker Spaniel** puppies out of a litter of six, from a mating of the mother with her father [184]. Clinical signs began around 3 to 4 weeks of age and included episodic behavioral changes, aimless running, and autonomic signs (salivation, urination, and defecation) that may reflect psychomotor seizures [184]. Bilateral pelvic limb proprioceptive deficits, forelimb hypermetria, bunny hopping, and absent menace response have also been noted. Results of hematology, blood chemistry, urinalysis, thyroid function, serum bile acids, blood ammonia levels, CSF analysis, and CT scans were all normal. Microscopic changes were characterized by spongy degeneration and associated diffuse gliosis mainly found in the gray matter, and were especially evident in the pons and cerebellar nuclei. Lesion intensity was less severe in other brainstem nuclei such as the dorsal and ventral thalamic nuclei and dorsal nuclei of the lateral geniculate body, as well as in the cerebral cortex and cerebellar cortex. Lesions were multifocal and always bilaterally symmetrical. Many spheroids were found in spongy areas as well as in normal neuropil. Demyelination (based on Luxol-fast blue staining) was found in internal capsule, thalamic tracts, cerebellar peduncles, cerebellar rubrothalamic tract, facial tract, and the trigeminal spinal tract. Axonal changes were mild. Immunohistochemical staining for canine distemper virus was negative. No lesions were found in the spinal cord.

Spongy degeneration of the CNS has been reported in two **Malinois Shepherd** crossbreed puppies [185]. Coarse tremors involving the head, limbs and trunk were observed at 3 weeks of age. The tremors were accentuated by excitement or voluntary movement but disappeared at rest and sleep. Other signs included wide-based stance, difficulty in maintaining balance, a tendency to move backwards or to the side while attempting to walk, and stilted, hypermetric gait. A fine oscillating tremor was observed in the eyes. Oculocephalic reflexes were delayed and postural reactions were slightly hypermetric. Spinal reflexes were normal. Hematology and blood chemistries were normal. Microscopic findings were characterized by a bilaterally symmetrical spongy state throughout the brain and spinal cord, with predominant involvement of the gray matter. All layers of the cerebral cortex were affected. Gray matter lesions were noted in basal nuclei, brainstem nuclei, cerebellar nuclei, and in lumbar and cervical intumescences of the spinal cord gray matter. White matter was relatively uninvolved, except for a spongy state and myelin loss in the cerebellar folia and some vacuolation in the cerebral cortical U-fiber region. The neuropil vacuoles were located adjacent to neurons, blood vessels, and glial cells. Neurons were not involved. There was no sign of necrosis, demyelination, or hypomyelination. Gliosis and marked astrocytic hypertrophy (shown by glial fibrillary acid protein staining) were evident. Axons appeared normal. Prognosis was considered to be poor.

A spongiform neurodegenerative disease has been recently reported in young **Rottweiler** dogs, of either sex, from North America, Europe, and Australia [160,186,187,219]. The condition is characterized by progressive signs of ataxia-dysmetria, especially apparent in the pelvic limbs, initially seen in puppies from 6 to 16 weeks of age, and progressing (sometimes over several months) to tetraparesis. Inspiratory stridor, associated with bilateral laryngeal paralysis, has been noted in several reports [160,186]. Absence of a gag reflex has also been reported [219]. Tendon reflexes are normal and there is no muscle atrophy in the limbs. In some affected dogs, ophthalmoscopy reveals persistent pupillary membranes on both irises and bilateral cataracts, and nystagmoid movements [160]. Behavioral changes, including aggression, absent-mindedness, and difficulty in training, have been noted in some dogs [186]. Analysis of CSF is normal, as are cervical radiography and myelography, ruling out vertebral malformation or injury. Thoracic radiographs show no evidence of megaesophagus. Electromyography may show abnormal spontaneous activity from the intrinsic musculature of the larynx, suggestive of denervation. At necropsy there is no gross abnormalities of the nervous system but atrophy of the dorsal cricoarytenoid muscles of the larynx has been noted in dogs with signs of laryngeal paralysis. Widespread histological abnormalities have been reported throughout the nervous system, including neuronal vacuolation (especially prominent in cerebellar roof nuclei and the nucleus of the spinal tract of the trigeminal nerve, but also in nuclei of the extrapyramidal system, thalamic nuclei, nucleus of the caudal colliculus, vestibular nuclei, medial cuneate nuclei, neurons of the spinal gray matter, dorsal root ganglia, and visceral ganglia), spongiform and microvesicular intra-axonal changes in the neuropil (in lateral vestibular nuclei, red nuclei, anterior colliculi, and dorsal root ganglia), and axonal degeneration which is most prominent in the spinal cord, especially severe in the thoracic segments, and most concentrated in the dorsolateral and ventromedial funiculi [160]. Wallerian degeneration in the spinocerebellar tracts may extend into the caudal brainstem, and in the central cerebellar gray and white matter. There is focally extensive degeneration and loss of Purkinje cells, Bergmann's gliosis, and presence of

axonal torpedoes in the granule cell layer. The dorsal cricoarytenoid muscles of the larynx show evidence of neurogenic atrophy, and nerve fascicles associated with this muscle (presumably from the recurrent laryngeal nerves) may have reduced numbers of axons. In one report, there was no sign of neuronal degeneration or loss in the nucleus ambiguus [160]. Wallerian-type degeneration has also been reported in sciatic nerves [186]. Ultrastructurally, the neuronal vacuoles are bound by a single membrane and are empty or contain granular material and sometimes membranous profiles [186,187,219]. Axosomatic and axodendritic synapses in affected neurons are intact both ultrastructurally and with synaptophysin immunostaining [187]. The cause of this condition remains unknown, although it is not considered to be a prion disease: immunoblotting and immunocytochemical staining of the brain for protease-resistant scrapie prion protein are negative [186,187,219]. A very similar (if not the same) condition has been described as an atypical form of neuroaxonal dystrophy in a 15 week old female Rottweiler with laryngeal paralysis [159].

A progressive spongiform neurodegenerative condition of the CNS has been reported in 5 related **Birman** kittens, of either sex [188]. All affected kittens were normal at birth. Clinical signs of progressive hind limb paresis and ataxia were first noted in animals from 2 to 6 months of age. The breeder noted that affected kittens had a very light coat color when born, were smaller in size than unaffected kittens, had smaller heads, and "closer-set" eyes, and a higher pitched meow. Kittens were bright and alert and 4 had bilateral cataracts. When walking, the hind limbs were excessively abducted with knuckling over on to the dorsal surface of the hind paws. Postural reactions were absent in the hind limbs and spinal reflexes were exaggerated. One cat had posterior paralysis and an absent menace response and gag reflex. Spinal reflexes and postural reactions were usually normal in the forelimbs, except in one cat with abnormal postural reactions on the right forelimb. This cat also had an inspiratory stridor and abnormal high-pitched meow. Hematology and blood chemistries were usually normal (2 cats had peripheral eosinophilia), as were CSF analysis (pressure, cell count, and protein levels), radiography, and motor nerve conduction velocity studies (performed in one cat). Microscopically, brains of all cats showed several large bilaterally symmetrical, disseminated foci of spongy change. These were often located in the gray matter of the cerebral cortex, and were especially marked in the piriform lobe where extensive vacuolation of the molecular layer extended into the pyramidal cell layer. Less severe foci were present in the inferior collicular nuclei of the midbrain. Vacuolation was also seen in the thalamus, cerebellar peduncles, oculomotor nucleus, and medulla oblongata. Vacuoles (from 10 to 50  $\mu$ m) were spherical or ovoid and typically present in clusters in the neuropil. Wallerian degeneration was observed in sensory and motor white matter tracts in the spinal cord. Ultrastructurally, the spongy change was associated with intramyelinic edema. Vacuoles were bound by one or more lamellae. Most were empty but a few contained loose whorled myelin figures. Peripheral nerves were normal. All kittens were inbred and an inherited etiology was suspected [188].

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## Myopathic Disorders (4-Feb-2003)

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### **Bouvier des Flandres Myopathy**

Familial Dysphagia

### **Central Core Myopathy**

### **Devon Rex Cat Hereditary Myopathy**

### **Exertional Myopathy**

### **Fibrotic Myopathy**

### **Glycogenosis**

### **Hepatozoon Myositis**

### **Hyperadrenocortical (Cushing's) Myopathy**

### **Hyperkalemic Myopathy**

### **Hypenatremic Myopathy**

### **Hypokalemic Myopathy**

### **Hypothyroid Myopathy**

### **Hypotrophic Myopathy**

### **Immobilization Myopathy**

### **Ischemic Neuromyopathy**

### **Labrador Retriever Hereditary Myopathy**

### **Limber Tail**

### **Malignant Hyperthermia**

Canine Stress Syndrome

### **Megaesophagus**

### **Mitochondrial Myopathy**

Clumber and Sussex Spaniel

Old English Sheepdog

Jack Russell Terrier

Labrador Retriever

Lipid Storage Myopathy

### **Muscular Dystrophy**

Canine Muscular Dystrophy

- Dystrophinopathies

Females

- Distal Myopathies

Feline Muscular Dystrophy

- Congenital Muscular Dystrophy

### **Myasthenia Gravis \***

Acquired Myasthenia Gravis

Congenital Myasthenia Gravis

### **Myositis**

Masticatory Myositis

Atrophic Myopathy/myositis

Polymyositis

Extraocular Myositis

Dermatomyositis

Myositis Ossificans

Laryngeal Myositis

Infectious Myositis

Paraneoplastic Myositis

Drug-induced Myositis

### **Myotonic Myopathy**

Myotonia Congenita

Adult-onset Myotonic Myopathy

Secondary Myotonia

### **Nemaline Myopathy**

### **Polyglucosan Myopathy**

### **Toxic Myopathy**

### **Vitamin E / Selenium-responsive Myopathy**

\* I have included a review of myasthenia gravis in this chapter. While this condition represents a junctionopathy, its inclusion here seems appropriate due to its clinical similarities with some myopathic disorders.

### Abbreviations -

ADH (adrenal-dependent hyperadrenocorticism); ALT (SGPT) alanine aminotransferase; AST (SGOT) aspartate aminotransferase; ATPase (myofibrillar adenosine triphosphatase); CK (creatine kinase); CSF (cerebrospinal fluid); CT (computed tomography); EMG (electromyography); HAC (hyperadrenocorticism); MRI (magnetic resonance imaging); NADH-TR (reduced nicotinamide adenine dinucleotide tetrazolium reductase); NCV (nerve conduction velocity); PAS (periodic acid-Schiff); PDH (pituitary-dependent hyperadrenocorticism).

### **Bouvier des Flandres Myopathy**

A degenerative myopathy has been reported in two female Bouvier des Flandres dogs [1]. Clinical signs were observed when dogs were about 2 years of age. Signs included regurgitation, exercise intolerance, generalized muscle atrophy, weakness, and a peculiar paddling gait characterized by overextension of the paws when walking. Cranial nerve function, postural reaction testing, and segmental spinal reflexes were normal. Contrast studies reveal megaesophagus. Serum creatine kinase (CK) levels were markedly elevated. Other hematological and blood chemistry values were normal. Electrodiagnostic testing demonstrated bizarre, high-frequency discharges in skeletal muscles. Motor nerve conduction velocities were normal. Muscle changes were characterized by moderate to pronounced fiber size variation associated with atrophic and hypertrophic fibers of both histochemical types (types 1 and 2), occasional giant-sized fibers with a whorled internal architecture and clefts, numerous internalized nuclei, multifocal necrosis, variable phagocytosis, basophilia, and marked increase in perimysial and endomysial fibrosis. These changes were seen in both limb and

esophageal muscle samples. Peripheral and intramuscular nerves were normal. Muscle biopsy samples taken from two clinically normal related dogs showed similar but less severe histopathological changes.

Prognosis is guarded to poor since the disease appears to progress rapidly. Corticosteroids given to one dog had no clinical effect. The clinical signs, elevated CK levels, and muscle pathology are similar to those seen in some dogs with muscular dystrophy.

A familial dysphagia, associated with megaesophagus, has been reported in Bouviers [2,3] mainly adults (age range: 6 months to 9 years), with histopathological findings in pharyngeal and/or esophageal muscle very similar to those described above, but without clinical signs of generalized weakness or exercise intolerance. In some Bouviers with megaesophagus, similar lesions were also observed in the masseter and temporalis muscles and in the intrinsic laryngeal muscles [2]. The EMG showed myopathic changes in oral/ pharyngeal/esophageal muscles. In 13 of 24 dogs, CK levels were elevated. This condition was considered to have similarities to oculopharyngeal muscular dystrophy in people, an autosomal dominant disorder characterized by progressive ptosis and dysphagia [4].

### **Central Core Myopathy**

A myopathy has been recognized in young Great Danes beginning around 6 months of age. Clinical signs of generalized weakness exacerbated by moderate exercise [5,6]. In one report, exercise or excitement associated with feeding would induce an episode of general body tremor and collapse into sternal recumbency, with rapid recovery after a few minutes rest [6]. Clinical weakness progressed in affected dogs, so that around 15 to 18 months of age, exercise intolerance was severe, with one dog unable to walk more than a few feet before collapsing. Elevated serum levels of CK, aspartate aminotransferase, and alanine aminotransferase have been reported. The condition is unresponsive to intravenous edrophonium chloride (Tensilon). EMG abnormalities include presence of positive sharp waves and fibrillation potentials in all muscles examined, including proximal and distal limb and trunk muscles. At necropsy, moderate atrophy of proximal limb and paraspinal muscles were noted in one dog [5]. Approximately 50% of muscle fibers contained a central core that occupied from 20 to 80% of the fiber. The cores appeared dark staining with hematoxylin and eosin stains, lacked cross-striations, and some contained vacuoles and nuclei. The cores were found in both type 1 and type 2 fibers. In longitudinal sections, the cores sometimes extended from 50 to 150  $\mu\text{m}$  along the fibers. The core structure varied from homogenous to finely granular or fibrillar. In Gomori trichrome stains, scattered rod-shaped bodies were seen. Scattered necrotic and regenerating (characterized by small basophilic fibers with subsarcolemmal nuclear chains) fibers were also observed. Ultrastructurally, the cores consisted of numerous mitochondria, glycogen granules and disarrayed, irregular filament bundles attached to thickened Z-lines. No abnormalities were seen in spinal cord, peripheral nerves, or intramuscular nerve branches. The condition has some similarities to certain congenital myopathies in people, including central core disease, an autosomal dominantly inherited disorder, although in humans there is an absence of oxidative enzyme activity in the cores, which consistently affect type 1 fibers [7]. Note that the cores resemble target fibers seen in denervating muscle [8], however unlike targets, cores extend along the length of the fiber [9]. In one dog, some clinical improvement occurred following oral prednisolone therapy, although signs quickly returned upon cessation of treatment [5]. Prognosis appears to be guarded to poor. The etiology of this myopathy is uncertain, although a possible genetic disorder involved with oxidative metabolism has been suggested [6].

### **Devon Rex Cat Hereditary Myopathy**

A degenerative, congenital myopathy, often called "spasticity" (albeit, erroneously), occurs in Devon rex cats and is believed to be inherited as an autosomal recessive trait [10-13]. Male and female cats are susceptible and signs may be seen in young cats around 4 to 7 weeks of age but may be delayed until 12 to 14 weeks. The most consistent clinical feature is passive ventroflexion of the head and neck, which is especially noticeable during locomotion, urination or defecation [12]. In severe cases, the chin is tucked into the sternum. Affected cats show a high-stepping forelimb gait, head bobbing, and with shoulder blades held high and the neck arched downwards. There is exercise intolerance often accompanied by progressive shortening of the stride and tremor. A "dog-begging" position is commonly observed. Some affected cats appear to have difficulty prehending and swallowing food, which may lead to upper airway obstruction. Regurgitation may be observed. Some cats have partial trismus. Clinical signs may be accentuated by concurrent illness, stress, or cold ambient temperature [12]. Apart from variable muscle atrophy seen in some cats, neurological testing is normal. Routine hematology and blood chemistries are normal, including serum CK levels. Radiographic and imaging studies reveal presence of megaesophagus and esophageal hypomotility, sometimes with gastroesophageal reflux [12]. EMG changes are mild and include variable presence of fibrillation potentials and positive sharp waves in muscles, particularly in triceps brachii and dorsal cervical muscles. No gross changes are seen in skeletal muscles. Microscopic changes in muscle include fiber size variation associated with hypertrophic and round/angular atrophic fibers, occasional fiber degeneration/regeneration, and variable presence of internal nuclei. In muscle samples from young cats, the muscle lesions tend to be mild and variable, but become more prominent with age and/or clinical severity [12]. There is no evidence of myositis or fiber type grouping. Dystrophin staining is normal. No abnormalities are seen in peripheral nerves, spinal cord, or brain. Mitochondrial enzyme assays in muscle are normal. The condition seems to stabilize around 9 months of age and affected cats may learn to cope with eating and drinking over time (feeding from a raised platform may be beneficial). Contractures do not occur. With adequate care, cats can thrive, although they may continue to tire

easily [10]. In some cats, prognosis may be guarded due to propensity to asphyxiation and laryngospasms associated with obstruction of the larynx/pharynx with food.

### **Exertional Myopathy**

Exertional myopathy, or exertional rhabdomyolysis (ER), is a disease that affects many animal species, including man [14]. It is an important complication commonly arising in newly captured wild animals and, in domestic animals, is most frequently encountered in horses, in whom the condition has been variously termed azoturia and paralytic myoglobinuria. The condition appears to be rare in cats. In dogs, exertional myopathy probably occurs most frequently in racing Greyhounds [15-18], although it is also common in sled dogs [19,20]. It has also been reported sporadically in dogs as a complication of prolonged convulsive seizures (and extreme muscle exertion) [21,533], babesiosis [22], malignant hyperthermia [23], and monensin-contaminated diets [24]. Rhabdomyolysis has been reported in dogs following experimental potassium and magnesium deficiency [25,26]. Rhabdomyolysis is occasionally seen in humans with lipid storage myopathies and defects of fatty acid oxidation [7]. The pathogenesis of ER is poorly understood since intensity and duration of muscle contraction are not the entire explanation [27]. Humidity and temperature may be factors in Greyhounds in Australia, and highly strung dogs that bark excessively and are overexcited at the track appear to be susceptible to developing rhabdomyolysis [15]. Results of a study performed during the 1998 Iditarod sled race showed no association between pre-race plasma vitamin E or total antioxidant status levels and risk of development of ER [19]. It has been suggested that mechanisms other than oxidative damage to muscles, such as repetitive trauma during eccentric exercise (e.g., running downhill), may be involved in initiating muscle damage and subsequent development of ER in sled dogs [19]. Energy for muscle metabolism is derived from blood glucose, muscle glycogen, and fatty acids (plasma free fatty acids, esterified fatty acids, and ketone bodies), while contributions from branched chain fatty acids and amino acids may increase with prolonged exercise [28]. Intense muscle exertion requires an adequate supply of glycogen (via glycolysis) and once depleted, the adenosinetriphosphate of muscle decreases leading to muscle cramps and muscle fiber necrosis. Sufficient muscle injury will lead to release of myoglobin (the red pigment responsible for the color of muscle) into the circulation and filtration through the renal glomerulus resulting in red-brown urine pigmentation and possibly, acute renal failure [29]. In racing greyhounds, severe lactic acidosis leading to muscle cell swelling, local ischemia, muscle cell necrosis and myoglobinuria with nephropathy has been proposed as a likely sequence of events in the pathogenesis of ER [15-17]. The nephropathy is considered to result from a mechanical obstruction of tubules by precipitated myoglobin [27]. Some Greyhounds have relapsing rhabdomyolysis without secondary renal involvement [18]. Clinical signs may occur during or within 24 - 48 hours of a race or trial and are characterized by extreme distress, hyperpnea, and generalized muscle pain, especially over the back and hindquarters, which may appear swollen and firm. Limbs may be rigidly tonic and affected dogs may have a "hunch-back" appearance and refuse to walk [15,17]. Myoglobinuria and death within 48 hours are common in severe, acute cases. There may be increased serum activities CK, aspartate aminotransferase (formerly SGOT), alanine aminotransferase (formerly SGPT), and lactate dehydrogenase; all of which may remain elevated for more than a week following an attack [15,17]. In one report on racing Greyhounds, presence of increased serum CK activities suggested possible subclinical muscle injury [30]. In the Iditarod study, blood CK activity was used to identify dogs withdrawn with exertional rhabdomyolysis (reference CK levels above which dogs were identified as having ER were > 10,000 IU/L, although some dogs had values > 400,000 IU/L) [19]. Interestingly, sled dogs prone to ER seem to develop the disorder early in the Iditarod race (e.g., within the first 500 miles) [19,20] and electrolyte disorders, such as hyponatremia (perhaps related to the high renal solute load associated with large energy intake) have been noted [19,20]. Hyponatremia (possibly from renal damage) and hyperkalemia have been reported in a Greyhound with ER [17]. Pathological findings in muscle include multifocal hemorrhage and myonecrosis that may involve 50 - 70% of muscle fibers [21]. Older lesions (several days) may show mineralization of necrotic muscle fibers, inflammatory infiltration by neutrophils, and sarcolemmal cell proliferation [14].

Prognosis depends on the severity of clinical signs. Dogs with hyperacute signs usually die within 48 hours from renal failure. Mortality rate is low in less severe cases that are treated with intravenous fluids, bicarbonate, anabolic steroids, antibiotics, body cooling, and rest [31]. Note that exertional rhabdomyolysis has certain features in common with stress-related malignant hyperthermia.

### **Fibrotic Myopathy**

This acquired, non-painful disorder associated with a fibrous band within a muscle has been reported sporadically in dogs - most commonly in German Shepherds, usually male, with an age range from 8 months to 9 years [32-38]. Other breeds include Doberman Pinscher, Rottweiler, Bobtail, St. Bernard, Boxer, and Old English Sheepdog. Fibrotic myopathy has recently been called gracilis or semitendinosus myopathy [37]. The etiopathogenesis of this condition is unclear. In humans, fibrotic myopathy may be congenital, although intramuscular injections have been implicated in some patients [39-41]. Active dogs seem to be susceptible to this disorder [32], and recent studies in dogs suggest that fibrotic myopathy may be related to muscle injury from excessive activity, including jumping and sprinting that can lead to muscle strain [38], with a suggested sequence of inflammation, edema, localized hemorrhage, and eventually fibrosis. Increased angulation (flexion) at the stifle in normal German Shepherds may predispose these dogs to increased

hamstring stress during physical activity [38]. While onset in some dogs is acute (compatible with grade 2 or 3 muscle injury), the lameness appears to be insidious in most dogs (compatible with chronic or grade 1 muscle strain) [38]. Apart from semitendinosus and gracilis muscles, fibrous bands may occur in quadriceps muscles, biceps femoris, and semimembranosus in hind limbs [32,38], as well as in supraspinatus and infraspinatus muscles in dogs [33,34]. A palpable band has also been found in the teres minor muscle (see below). Duration of signs may range from weeks or several years [38].

Fibrotic myopathy of the semitendinosus muscle is associated with a palpable thickened fibrous band that may extend from the tuber ischii to the tibia within the belly of the semitendinosus muscle. Tight fibrous cords are also palpable in affected gracilis muscles extending from the midline of the pelvis to the caudomedial aspect of the stifle. In dogs with gracilis and/or semitendinosus muscle involvement, the hind-limb gait is characterized by a shortened stride with a rapid, elastic medial rotation of the paw, external rotation of the hock, and internal rotation of the stifle during the mid-to-late swing phase of the stride [35,37]. Kinematic analysis indicate that the range of motion of the stifle is reduced [42]. The gait anomaly results from restricted abduction of the coxofemoral joint and reduced extension of the stifle and hock. Note that the lameness is best appreciated at the trot. Bilateral involvement (of the gracilis or semitendinosus muscle) is commonly encountered, with reports varying from 39% to 61% of affected dogs [37,38], while both muscles may be involved ipsilaterally or contralaterally [35,36]. Histologically, the band consists of an abundance of dense collagenous connective tissue, with a distinct interface between connective tissue and muscle bundles. Morphological studies in our laboratory or in others have not identified primary muscle or peripheral nerve disease, although variable myofiber degeneration around the periphery of the fibrotic band has been seen occasionally, sometimes associated with mild mononuclear cell inflammation and focal hemorrhage [37]. The replacement of muscle fibers with dense collagenous connective tissue results in a mechanical lameness resulting from failure to fully extend the limb. Neurological examination is usually normal; however, pressure applied to the affected muscle, abduction of the coxofemoral joints of affected limbs, and extension of stifle/talocrural joints in affected limbs may elicit pain [37]. Serum CK levels may be normal or moderately elevated in some animals [35,43]. Absence of myoelectrical activity in the band during EMG evaluation is consistent with total replacement of muscle fibers by dense connective tissue [35,43]; however, spontaneous EMG activity in the vicinity of the band suggests recent muscle damage [38]. In occasional dogs, fibrillation potentials and rare myotonic discharges have been recorded [35,36]. Imaging techniques have been used to identify the intramuscular fibrous cords in people [44]. Soft-tissue swellings associated with the myotendinous areas of affected muscles may be detected on radiographs, and two-dimensional ultrasonography in one dog revealed increased size and reduced homogeneity of the gracilis muscle, with an enlarged tendon of insertion compared to the normal muscle [37]. Prognosis is guarded to poor since the condition in dogs tends to recur within several months following surgical resection of the fibrous band, or transection, partial excision, or complete resection of the affected muscle [37]. Non-surgical treatment (e.g., corticosteroids, non-steroidal inflammatory drugs, acupuncture) is usually ineffective. Non-surgical rehabilitation, including therapeutic ultrasound and cross-fiber friction massage, resulted in mild improvement in several dogs (slight increase in range of motion of the stifle and less crossing over of pelvic limbs) [38]. If fibrotic myopathy is causally related to muscle strain, appropriate preventive measures might include stretching, warm up exercises, and gradual build up to more intensive activities [38]. Inability to maintain the affected leg in extension during healing might contribute to recurrences [38]. The suggestion that oxygen-free radicals cause pericytic necrosis and fibroblastic proliferation in some forms of human fibrotic disorders may offer therapeutic possibilities [45].

Post-traumatic fibrotic myopathy has also been reported in an 18 month old female Dalmatian together with myositis ossificans [46]. Clinically, there was markedly reduced range of motion of hip extension and stifle flexion, and a firm mass beneath the sartorius muscle in the region of the rectus femoris muscle. Surgical studies revealed replacement of the rectus femoris muscle by a white fibrous band that was histologically characterized by dense fibroblastic connective tissue. A firm calcified mass was found on the iliac shaft. Immediately upon resection of the fibrous band, the coxofemoral and stifle joints were returned to a normal range of motion. No recurrence of lameness was seen after 6 months.

More recently, teres minor myopathy causing sudden onset left forelimb lameness of 8 month's duration was reported in a 5 year old working Labrador Retriever [47]. Minimal circumduction was present in the left forelimb and the left suprascapular muscles were atrophied. A painful palpable band-like structure was found in the region of the teres minor muscle. Ultrasonography revealed an area of increased echogenicity within this band. EMG studies were normal. Exploratory surgery identified the band to be the teres minor muscle, which was adhered to the joint capsule and infraspinatus/deltoid muscles. Histological examination revealed focal areas of inflammation with mononuclear cells, floccular degeneration of contractile elements, patchy regeneration, but surprisingly, without significant fibrosis. Following excision of the teres minor muscle, there was complete resolution of the lameness with no apparent adverse effects on joint function. The etiology of this condition was not determined although trauma was suspected to be the initiating factor. A comparable condition involving the semitendinosus muscle was reported in a mature castrated male Himalayan cat [43] in which the lameness was characterized by marked flexion of the hip, stifle, and hock as the limb was advanced. Since the limb could not be fully extended, the paw was placed abruptly, sometimes with knuckling. A single injection of methylprednisolone acetate (10 mg, IM) had no discernible effect. Surgical exploration indicated that the semitendinosus muscle was firm, white, and cord-like. Tenorrhaphy produced a favorable long-term response (1 year after surgery, the cat's gait remained abnormal but had little effect on ambulation).

## Glycogenosis

Several glycogen storage diseases may result in weakness and muscle changes, including type II, III, IV, and VII glycogenoses (see glycogenosis).

## Hepatozoon Myositis

This disease is caused by *Hepatozoon canis*, a protozoan organism that infects dogs [48-51], and rarely, cats [52]. It is transmitted primarily by the tick *Rhipicephalus sanguineus*. The disease has a world-wide distribution [53-56], although the North American strain of *H. canis*, seems clinically distinct from those in other parts of the world in which signs tend to be subclinical [57,58]. Indeed, the North American strain has recently been identified as *Hepatozoon americanum*, a species of the apicomplexan protozoan parasite [59,532]. The definitive host for *H. americanum* is believed to be the tick *Amblyomma maculatum* [60,61]. In the U.S., most cases are reported from the Gulf Coast region of Texas and Louisiana, and Oklahoma, but recent reports extend the range to Georgia and Alabama [62]. Infection occurs by ingestion of an infected tick [58]. Sporozoites are released in the intestine of the dog, penetrate the intestine and spread via the blood or lymph to various tissues where they undergo schizogony. Merozoites are released from schizonts. Merozoites that enter leukocytes become gametocytes. Infection of blood-sucking ticks occurs by ingestion of infected leukocytes. Vertical transmission has been reported in puppies [63].

Commonly reported clinical signs of *H. americanum* include fever (unresponsive to antibiotics), lethargy, weight loss, anorexia, depression, muscular hyperesthesia (especially over paraspinal areas), paraparesis or paralysis, bloody diarrhea, mild anemia and purulent ocular and nasal discharges. Glossitis, pharyngitis, and skin lesions have also been reported. Hyperesthetic animals may be reluctant to move and often assume a sitting posture with rigidity of the trunk and neck ("master's voice" posture) [58]. Temporal muscle atrophy may be present. Concurrent infection or immunosuppression may facilitate infection and accelerate development of clinical signs. Young dogs (< 6 months of age) appear most susceptible to infection. The clinical course may be prolonged with spontaneous remissions and intermittent periods of fever and pain.

Laboratory findings include neutrophilic leukocytosis (ranging from 20,000 to more than 200,000 cells/ $\mu$ l), occasional eosinophilia and basophilia, mild regenerative anemia, low serum glucose (probably an artifact associated with the extreme neutrophilia [58]) and albumin levels, increased serum alkaline phosphatase and increased inorganic phosphorus concentrations [62]. Analysis of CSF from affected dogs may reveal neutrophilic pleocytosis (e.g., > 300 WBCs/ $\mu$ l) and increased protein levels (e.g., > 100 mg/dl) [64]. Radiography may demonstrate pronounced periosteal bone proliferation and/or smooth laminar thickening of the periosteum affecting any bone except the skull, although the diaphysis of the more proximal long bones of the limbs is commonly involved [65]. EMG studies reveal abnormal spontaneous potentials.

Muscle biopsy is often useful in establishing a diagnosis [50,62,66] - changes include myositis and pyogranulomas composed of macrophages, neutrophils, and occasionally eosinophils, sometimes adjacent to large, thin-walled cysts (schizonts) approximately 250 - 500  $\mu$ m in diameter (pain, fever, and periosteal bone proliferation may be a consequence of the polymyositis). The nuclei of the cysts are surrounded by host-derived bluish, mucinous mucopolysaccharide material associated with fine lamellar membranes [66,67]. Some cysts contain numerous small, round, basophilic bodies considered to be micromerozoites. Tissue stages of *H. americanum* may be identified in tissue sections using immunohistochemical techniques [68]. Organisms can be seen within neutrophils and monocytes in Romanovsky-stained peripheral blood smears [49,57,58]. At necropsy, gross visible pyogranulomas may be seen in cardiac and skeletal muscles (including extraocular muscles), smooth muscle, liver, skin, lymph nodes, lung, and kidney [57]. Glomerulonephritis, amyloidosis, and the nephrotic syndrome are commonly found [57]. An indirect enzyme-linked immunosorbent assay (ELISA) has recently been reported to be a reliable tool for diagnosing American canine hepatozoonosis [69].

Until recently, no antiprotozoal agents consistently caused long-term remission of signs, and most infected dogs could be expected to die within 2 years of clinical diagnosis [58]. Temporary remission of signs for several months had been achieved by administering trimethoprim sulfadiazine (15 mg/kg PO bid), clindamycin (10 mg/kg PO tid), and pyrimethamine (0.25 mg/kg PO sid) (TCP) for 2 weeks [62]. Aspirin given at 5 mg/kg PO bid for several days was helpful in reducing the fever. Temporary remissions had also been achieved using toltrazuril at 5 mg/kg PO bid for 5 days [62], a drug no longer available for clinical use in the United States. The initial favorable response to TCP is typically followed by periodic relapses that subsequently result in chronic debilitation leading to renal failure, death, or euthanasia. Corticosteroids frequently exacerbate clinical signs or induce a recurrence of signs. However, in a recent study, treatment of affected dogs with TCP for 2 weeks followed by long-term administration of decoquinate, a quinoline anticoccidial agent at 10 to 20 mg/kg, every 12 hours mixed in food (the drug is available from feed stores in 50-lb bags, and the dosage is 0.5 to 1.0 teaspoon/10 kg, mixed in food, twice daily) has increased survival time (> 33 months) without any deleterious side-effects [70]. Continuous treatment with decoquinate for 2 years is being recommended. Note that decoquinate is ineffective in dogs with advanced disease/glomerulonephropathy at the time treatment is begun. Control of ticks by routine dipping of dogs from infected areas will help to limit spread of the disease and reinfestation of susceptible hosts [51]. Hepatozoonosis does not appear to be an important public health concern.

## Hyperadrenocortical (Cushing's) Myopathy

An acquired degenerative myopathy has been reported in dogs in association with hyperadrenocorticism (Cushing's disease) [71-75]. Several forms of hyperadrenocorticism (HAC) exist and are listed below, all of which are characterized by chronic high serum cortisol (glucocorticoid) concentrations [76]:

1. **Pituitary-dependent HAC (PDH)** - Often accompanied by tumors of the adenohypophysis that produce ACTH or a similar acting hormone. Eighty percent or more of cases of pituitary Cushing's disease are reportedly associated with a pituitary tumor. These tumors may stem from the pars distalis (80%) or the pars intermedia (20%), since both regions contain cells that are capable of producing adrenocorticotrophic hormone (ACTH). This form of HAC is most frequently associated with bilateral adrenocortical hyperplasia. If the hypothalamus is disrupted by the tumor, signs of a hypothalamic syndrome may accompany signs of HAC (see pituitary tumor). Approximately 75% of dogs with PDH weigh < 20 kg and Poodles, Beagles, German Shepherds, Dachshunds, and Terrier breeds appear overrepresented [76,77].
2. **Adrenal-dependent HAC (ADH)** - Usually associated with primary adrenocortical neoplasia (adenoma or carcinoma) with contralateral adrenocortical atrophy, and which occurs in approximately 10 to 20% of dogs with HAC [77]. Occasionally, tumors may involve both adrenal glands. Poodles, German Shepherds, Dachshunds, Terrier breeds, and Labrador Retrievers appear overrepresented in dogs with adrenal tumors and approximately 50% of dogs weigh > 20 kg [76,77].
3. **Iatrogenic HAC** - Associated with excessive/prolonged corticosteroid administration, especially fluorinated agents such as triamcinalone, betamethasone, and dexamethasone [78]. It is usually associated with bilateral adrenocortical atrophy. Interestingly, a presumed glucocorticoid-induced myopathy was reported in a dog receiving ophthalmic corticosteroid therapy that was associated with adrenal suppression [79].

Clinical signs of HAC include panting, polydipsia, polyuria (due to a reversible form of central diabetes insipidus), bilaterally symmetrical alopecia, pendulous abdomen, hyperpigmentation, comedones, and hepatomegaly [76]. Myopathic signs may include gradual development of a stiff, stilted gait, weakness, stumbling, and generalized muscle atrophy that is often marked in epaxial, temporal, and masseter muscles [71-75]. Proximal limb muscles may appear enlarged and bulging in some dogs [72]. Pelvic limb rigidity, especially in middle-aged and older dogs, especially Poodles, is not unusual. Some hyperadrenocorticoid dogs have a form of myotonia with signs of muscle dimpling and myotonic-like discharges seen on EMG (see below), generalized increase in muscle tone, rigid epaxial muscles, arching of the back, ears drawn back, and tongue protrusion [71,72,75]. Feldman states that myotonic-like stiffness occurred in only 5 of 800 dogs with Cushing's syndrome in his practice [80]. Tendon reflexes are usually normal. Gastrocnemius muscle rupture, believed to be associated with the underlying myopathy, was reported in a 6 year old spayed female Shetland Sheepdog with iatrogenic HAC [81]. Note that one potential complication of HAC is thromboembolism, possibly related to coagulation protein loss in urine [76], and signs of pelvic limb weakness, pain and collapse as a result of occlusion of the distal aorta and/or the iliac arteries [82]. Electromyographic studies of proximal and distal limb muscles and paraspinal muscles may reveal evidence of bizarre high frequency discharges, often producing a "dive-bomber" sound. The discharges may wax and wane in amplitude and frequency suggesting they represent myotonic potentials [75], although in most dogs with hyperadrenocorticoid myopathy, the discharges do not wax and wane and are termed pseudomyotonic potentials (See Electrodiagnostics). It has been suggested that pseudomyotonia in French Poodles is not a simple consequence of HAC but a separate, possibly genetic, disease [524]. In one recent study of 30 dogs with HAC, complex-repetitive discharges were recorded that were more prominent in proximal appendicular muscles while fibrillation potentials and positive sharp waves were found in 60% of affected dogs and localized in the distal limb muscles [525]. Myotonic discharges were not found in this study. Nerve conduction studies may be normal or slowed (see hyperadrenocortical neuropathy).

Diagnosis of hyperadrenocortical myopathy is based on laboratory data, signalment (mature, female Poodles may be predisposed to the myopathy), clinical and electrodiagnostic findings, and muscle biopsy. Laboratory findings include "stress" blood count (lymphopenia, eosinopenia, neutrophilia, and monocytosis), increased serum alkaline phosphatase (in dogs), hyperglycemia (usually lower than renal threshold in dogs), hypercholesterolemia and lipemia from the glucocorticoid-induced lipolysis, and reversible (usually) hypertension in dogs [76,83]. Serum CK activity may be elevated [72,75]. Histological findings include mild degenerative changes associated with fiber size variation, presence of subsarcolemmal masses, focal necrosis and fiber splitting, target fibres or fibres with "central areas", and fiber atrophy, especially of type 2 fibers [71,73]. Fiber grouping may be present, and in some dogs, we have seen demyelination/remyelination in peripheral nerves (see hyperadrenocortical neuropathy). Ultrastructural changes in muscle include splitting and disorientation of myofibrils, disruption of mitochondrial cristae, subsarcolemal and intermyofibrillar aggregates of mitochondria, presence of large bizarre-shaped mitochondria, increased numbers of intermyofibrillar vacuoles, small increase in sarcoplasmic glycogen deposition, and variable dilatation of the sarcotubular system [73,84].

The pathophysiologic basis for hyperadrenocortical myopathy is unknown, although the changes probably result from excessive circulating glucocorticoids and muscle protein catabolism, since identical muscle changes are observed in dogs

and cats receiving corticosteroids [72,73,84,85]. Muscle weakness and atrophy are believed to be mediated by the glucocorticoid induction of the enzyme glutamine synthetase [86,87], and the increased glutamine synthetase activity may be reduced by growth hormone or insulin-like growth factor [87]. It was proposed that selective muscle atrophy (i.e. type 2 fibers) may result from differences in myofiber glucocorticoid sensitivity [88], although density of glucocorticoid receptors appears to be comparable in different muscle fiber types [89]. In people with Cushing's disease, ACTH excess may also be directly myopathic [90]. Specific findings for the different forms of HAC are as follows [77,91].

1. Pituitary-dependent HAC (PDH) - Normal or high baseline plasma cortisol and ACTH levels; exaggerated cortisol response to ACTH stimulation; and suppression of plasma cortisol with high-dose (but not low-dose) dexamethasone. Approximately 20 - 30% of dogs with this form of HAC are resistant to dexamethasone suppression.
2. Adrenal-dependent HAC (ADH) - Normal or high baseline plasma cortisol; normal or exaggerated cortisol response to ACTH stimulation; failure to suppress plasma cortisol with any dose of dexamethasone; and undetectable plasma ACTH concentration.
3. Iatrogenic HAC - Normal or low baseline plasma cortisol; little or no cortisol response to exogenous ACTH; and undetectable plasma ACTH concentration [76,92].

In one review, the most sensitive tests in distinguishing dogs with pituitary-dependent HAC from dogs with adrenocortical tumors were the plasma endogenous ACTH concentrations, abdominal radiography, and abdominal ultrasonography, although none of the tests alone were completely reliable [77]. Recently, however, a single determination of endogenous plasma ACTH levels and adrenal ultrasonography were considered to be discriminatory in a prospective study to differentiate between PDH and ADH and more accurate than dexamethasone suppression testing [93]. Ultrasonography appears to be a reliable test for functional adrenocortical tumors [94]. The number of PDH dogs with macroadenomas is probably higher than the literature suggests [95]; however, on the basis of endocrine test results, dogs with PDH and large pituitary tumors cannot be adequately distinguished from dogs with PDH and microscopic pituitary tumors prior to onset of clinical signs [95]. Nevertheless, it has been suggested that inadequate serum cortisol suppression during high-dose dexamethasone suppression testing in dogs with PDH, may be a prognostic indicator for subsequent development of an invasive pituitary tumor [96]. It should be noted that pituitary and adrenal tumors can coexist in dogs with HAC, leading to a confusion of test results and complicating diagnosis and treatment [97]. Note also that diabetes mellitus can be a complication of HAC, especially in cats, and that dogs with a reduced beta cell mass prior to development of HAC are more likely to develop concurrent diabetes or to develop diabetes with glucocorticoid administration (Dr. Richard Nelson, University of California-Davis, personal communications, 2002).

Myopathic signs may abate following surgical or medical management of the hyperadrenocorticism [76,98-101]. Several treatments used in the medical management of PDH and ADH in dogs include mitotane (a potent adrenocorticolytic drug that causes necrosis of the zona fasciculata and reticularis, and thus effects "medical adrenalectomy"), and ketoconazole (a drug that inhibits steroid biosynthesis and suppresses cortisol secretion with minimal effects on mineralocorticoid production) [101]. L- deprenyl (Anipryl) thought to control Cushing's by downregulating ACTH via enhanced brain dopamine levels [76], is not recommended as the sole treatment for canine PDH [102]. Other clinicians do not recommend it at all [76]. Another potentially useful drug for treating dogs with PDH or ADH is trilostane, which interferes with adrenal steroid biosynthesis [103].

Note that withdrawing or reducing the dose of the glucocorticoid is the primary method of treating steroid myopathy, or using non-fluorinated steroids since steroid myopathy is most often associated with fluorinated steroids (e.g., triamcinalone, betamethasone, and dexamethasone) [104,105].

Prognosis is guarded in dogs with HAC if contractures and severe muscle atrophy are present in pelvic limbs. Myotonic signs may progress despite effective mitotane therapy, in which case procainamide administration (e.g., at 12.5 mg/kg PO bid) may reduce the myotonic stiffness [75]. Exercise programs and physical therapy may assist recovery and probably should be encouraged in any animals receiving glucocorticoids.

### **Hyperkalemic Myopathy**

Increased serum potassium values may occur in association with adrenocortical insufficiency, diabetes mellitus, acute renal failure, or severe acidosis (see feline muscular dystrophy). In conjunction with the characteristic signs of these diseases, animals may manifest episodic weakness, loss of strength and tendon reflexes due to increased intracellular positivity (with hyperkalemia, the chemical gradient for potassium efflux is decreased) to the point that resting membrane potential falls below the threshold potential with subsequent minimal depolarization and less excitable membranes [106,107]. Muscle weakness with hyperkalemia typically occurs with serum potassium levels > 8 mEq/l [535]. Diagnostic aids include serum potassium and sodium, plasma cortisol, ACTH response testing, blood glucose, blood urea nitrogen, urinalysis, creatinine, and blood pH values.

Hyperkalemic periodic paralysis (HPP) is a rare disorder in dogs that is characterized by episodic weakness, limp neck, protruding tongue, collapse and paralysis and may be precipitated by exercise and/or excitement [108]. Attacks lasted 10

to 15 seconds after which the animal appeared drowsy but quickly resume normal behavior. Attacks were also precipitated by oral potassium administration. No changes in serum glucose or lactate levels were found. In humans, the pathogenesis of this disorder is associated with a sodium channelopathy, an inherited disorder resulting in reduced inactivation of the sodium channel, leading to increased muscle cell permeability to sodium and muscle membrane hypoexcitability, and episodic weakness [109,110]. The sodium current, through noninactivating channels, may cause the skeletal muscle weakness in HPP by depolarizing the cell, thereby inactivating normal sodium channels, which are then unable to generate an action potential. In addition, myotonic potentials may occur as a result of a small depolarization and repetitive excitation (see also, myotonic myopathy) [110]. Thus, the hyperkalemia appears to be the consequence rather than the cause of the periodic paralysis [9]. A very similar condition occurs in horses as an autosomal codominant genetic disease [111]. Attacks are usually associated with increased plasma potassium levels. Focal necrosis and variable vacuolar changes may be seen in skeletal muscle fibers. EMG abnormalities may be detected, including prolonged insertional activity, complex repetitive discharges, spontaneous activity and myotonic discharges [112]. Treatment with acetazolamide, 2 mg/kg, bid, PO, was beneficial in treating the 7 month old Pit Bull with HPP [108]. Acetazolamide is a thiazide derivative and carbonic anhydrase inhibitor that promotes renal loss of sodium and potassium. In humans with HPP, thiazide diuretics are effective [9].

### **Hypernatremic Myopathy**

Episodic weakness and signs of depression were reported in a 7 month old Domestic Shorthaired cat with episodic hypernatremia (serum Na concentration ranging from 182 to 215 mEq/L; normal is 148 to 161 mEq/L) secondary to hypodipsia (failure to drink water) [113]. This rare condition was accompanied by hyperosmolality (ranging from 381 to 431 mOsm/L) and evidence of hypopituitarism (adrenocorticotrophic and growth hormone deficiencies, along with blunted thyroxine response to thyroid-stimulating hormone). The most prominent clinical sign was ventroflexion of the neck. No other neurological abnormalities were detected. Electromyographic testing revealed prolonged insertional activity, fibrillation potentials, positive sharp waves, and bizarre high-frequency discharges. Nerve conduction velocities were normal. These abnormalities were more severe during episodes of hypernatremia. Serum creatine kinase activity was increased, while CSF analysis was normal. Examination of several muscle biopsies were normal. Contrast-enhanced computed tomographic studies of the brain demonstrated marked hydrocephalus, although no hypothalamic or pituitary lesions were detected. The episodic weakness might have been associated with muscle membrane alterations associated with displacement of intracellular potassium by high levels of extracellular sodium. Interestingly, the clinical signs, serum CK levels, electrodiagnostic data, and muscle biopsy findings were very similar to those seen in cats with hypokalemic myopathy. Forced water intake and dietary sodium restriction (using a low-salt feline diet) corrected the hypernatremia and signs of muscle dysfunction. After restoration of eunatraemia, secretion of pituitary hormones became normal. It was suggested that hypothalamic dysfunction, possibly related to hydrocephalus, induced both hypodipsia and transient hypopituitarism [113].

### **Hypokalemic Myopathy**

Hypokalemic myopathy is a metabolic disorder of older cats that has been linked with chronic renal disease and excessive urinary potassium loss [114-116], although a similar, if not identical disease, was reported in 1984 [117]. Synonyms are feline kaliopenic polymyopathy-nephropathy syndrome, and sporadic feline hypokalemic polymyopathy. Low dietary potassium intake secondary to inadequate potassium levels in certain commercial rations has been associated with episodic hypokalemic myopathy [114,118]. Additionally, potassium urinary loss may be exacerbated by some diets that are acidified to reduce development of crystalluria and urolithiasis. It has been suggested that increased potassium loss induced by renal dysfunction may represent a phenomenon peculiar to cats [115]. Furthermore, chronic potassium depletion (e.g., from deficient rations) may lead to progressive renal disease (associated with renal ischemia, increased renal ammoniogenesis, activation of the alternate complement pathway, and tubulointerstitial injury) as well as sudden changes in muscle membrane sodium permeability [114]. Decreased extracellular potassium levels will produce an increase in resting membrane potential, resulting in a greater difference between resting and threshold potential necessary for muscle contraction [119]. This lessened state of electrical excitability underlies the muscle weakness [107]. Additionally, hypokalemia may negatively affect insulin release and end-organ sensitivity to insulin [106]. Other causes of hypokalemia include gastrointestinal loss of potassium, post-obstructive diuresis following relief of urethral obstruction in cats, administration of loop or thiazide diuretics, and rarely, mineralocorticoid excess [535]. Clinical signs are characterized by acute onset of a stiff-stilted gait, reluctance to walk, exercise intolerance, ventroflexion of the neck (especially in cats), and muscle pain. Spinal reflexes may be depressed. Serum CK levels are moderately to markedly elevated, while serum potassium values are low (e.g., < 4.0 mEq/L). Serum creatinine levels may be markedly increased. In the hypokalemic cats fed a high protein vegetarian diet, plasma taurine concentrations decreased and glutamic acid increased markedly [118]. Mild, diffuse electromyographic changes (e.g., presence of positive sharp waves) have been recorded in various skeletal muscles. Light microscopic evaluation of muscle samples is usually normal, although myofiber vacuolation and mild myonecrosis may occasionally be observed. Ultrastructural changes in people indicate that the vacuoles are membrane-bound and reveal the frequent presence of tubular aggregates that selectively involve type 2 fibers [120]. Rhabdomyolysis in severe hypokalemia might be related to osmotic



expansion of cells due to increased intracellular sodium and chloride levels or reflect ischemic myonecrosis due to decreased muscle blood flow associated with impaired potassium metabolism during muscle contraction/exercise [106,114].

Prognosis is guarded to favorable and may depend upon the severity of the underlying renal disease, if present. Most cats reportedly show significant improvement in muscle strength within 2 to 3 days of initiation of treatment. Oral potassium supplementation (e.g., potassium gluconate - Tumil-K<sup>™</sup>, Daniels Pharmaceuticals), at 5 to 10 mEq/ cat /day, divided bid, is recommended for severely hypokalemic cats. For less severely affected animals, 2 to 4 mEq/day is usually adequate. Permanent daily supplementation with regular re-evaluation of serum potassium, serum creatinine, and urinary potassium loss is recommended, since cats that are not supplemented have a tendency to become hypokalemic again.

Severe hypokalemia and generalized flaccid paralysis has been reported in a 6 year old female Miniature Poodle after furosemide administration for suspected congestive heart failure [121]. In this case, hypokalemia presumably resulted from an increased flow rate in the distal tubules and increased secretion of aldosterone secondary to volume depletion caused by the thiazide diuretic. Muscle biopsies showed severe myonecrosis, phagocytosis, fiber splitting, internalized nuclei, and atrophy/hypertrophy. Peripheral nerve biopsy was normal. After treatment of the hypokalemia (intravenous fluids and potassium supplementation), the dog was clinically normal within 16 days of complete paralysis, while muscle biopsies were normal within 30 days.

Note that hypokalemia may also result from various metabolic and endocrine disorders [122]. In one report, hypokalemic myopathy occurred in 9 cats as a result of severe diabetic ketoacidosis and its therapy (e.g., hypokalemia may result from the attendant osmotic diuresis, correction of the acidosis, or insulin-mediated cell uptake) [123]. In this study, normokalemia and the myopathy resolved within a few days of potassium supplementation. Acute onset of muscular weakness and ventroflexion of the neck have been reported in several hyperthyroid cats in association with hypokalemia, the cause of which was not determined [13,119,124]. Cats responded quickly to potassium supplementation or following resolution of the hyperthyroidism. In humans, nonfamilial hypokalemic thyrotoxic periodic paralysis is commonly seen among Asians [125,126]. It has been reported that sudden paralysis occurring while at rest after a large carbohydrate meal or strenuous exercise is a common presentation and that intracellular shifts of potassium triggered or facilitated by hyperthyroidism and hyperinsulinemia are the biochemical features [126,127]. Correction of the hyperthyroidism is the definitive treatment in people. A periodic myopathy characterized by muscle stiffness, weakness, and pain secondary to persistent hypokalemia and metabolic alkalosis has been reported in a German Shepherd with an hepatic neuroendocrine carcinoma, thought to be a primary hepatic carcinoid [128]. Ectopic adrenocorticotrophin hormone secretion was suspected as the cause of hypercortisolism and hypokalemia (possibly associated with cortisol inactivation overload). Note that in most dogs with hyperadrenocorticism, hypokalemia is either not seen or is mild and clinically insignificant [76]. Hypokalemia secondary to an aldosterone producing tumor of the adrenal gland (Conn's syndrome) has been observed in cats [13]. Aldosterone normally regulates electrolyte/fluid balance by facilitating sodium retention and potassium excretion. Clinical signs included intermittent muscle weakness and collapse that became progressively more severe. Blood biochemical studies revealed elevated aldosterone levels and high serum creatine kinase levels. Temporary improvement resulted from administration of spironolactone at 10 - 100 mg PO daily.

A second type of hypokalemic myopathy has been reported in young Burmese kittens, 2 to 6 months of age [129-131], although the disorder has also been reported in a 2 year old Burmese cat [132]. This condition is considered to be a homozygote recessive hereditary disease and is characterized by periodic muscle weakness and ventroflexion of the neck associated with intermittent hypokalemia (e.g., < 3.0 mEq/L) and increased serum creatine kinase values, sometimes reaching very high values, e.g., > 50,000 - 90,000 IU/L [129,131]. The condition has also been termed periodic hypokalemic myopathy [132]. Attacks occur suddenly and are transient and may be precipitated by stress or vigorous exercise. The variable clinical course is characterized by improvement followed by relapse, and there may be weeks between episodes. A head tremor is seen in some cats. Cats are reluctant to walk and tire easily, have a stiff, stilted gait with thoracic limb hypermetria, and a wide-based stance in the hind limbs. Carpal knuckling can be a distinctive clinical feature and some cats sink on their hocks [129]. There are only minor electromyographic and histopathologic changes seen in muscle. Neither decreased potassium intake nor increased renal potassium loss have been found in affected Burmese cats. Continued dietary supplementation of oral potassium usually produces a favorable response (e.g., potassium gluconate solution at 2 to 4 mEq or mmol/cat PO daily, until serum potassium levels are stable) [133]. Some kittens improve without treatment. The periodic hypokalemic attacks in these cats are similar to those seen in humans with hypokalemic periodic paralysis, an inherited calcium channelopathy disorder associated with abnormal muscle membrane excitability and influx of potassium into the muscle fiber that causes muscle fiber depolarization and inexcitability [9]. Patients have an increased sensitivity to insulin moving potassium into cells.

### **Hypothyroid Myopathy**

Myopathies have been reported infrequently in mature dogs with primary hypothyroidism [134]. Clinical signs of bilaterally symmetrical flank alopecia and obesity are often associated with the hypothyroidism. Presence of lethargy, weakness, and reduced exercise tolerance in some dogs with chronic hypothyroidism may reflect the underlying myopathy [135]. A polymyopathy has been seen in several dogs with megaesophagus and myasthenia gravis [136]. We have seen myotonic-like discharges in muscles of some hypothyroid dogs on EMG studies [137]. In people, skeletal

muscle changes may precede clinical and laboratory evidence of hypothyroidism [138]. The etiopathogenesis of this endocrine myopathy is unknown. A disturbance in carbohydrate metabolism has been proposed to explain the preferential type 2 fiber atrophy which occurs in human and canine muscle [139]. In hypothyroid people, phosphorus magnetic resonance spectroscopy studies suggested a defect of the high energy phosphate metabolism (lower phosphocreatine recovery rate) reflecting probable mitochondrial metabolism impairment [140]. Muscle glycogenolysis is impaired that may result in fasting hypoglycemia in human patients, and there is net protein catabolism [105]. Atrophic type II fibers are oval or angular in outline and are distributed throughout all muscle fascicles. A deficiency of type II fibers has also been noted in some dogs. Variable fiber hypertrophy may be present and nemaline rod inclusions may be observed in some muscle fibers, especially in type I fibers. No cellular response or myodegeneration is seen and intramuscular and peripheral nerves are normal. In people, internal nuclei may be increased, along with glycogen and mitochondrial aggregates, dilated sarcoplasmic reticulum, proliferating T-system profiles, and focal myofibrillar loss [120]. More recently, muscle fiber cores have been found in needle biopsies in people [141]. Reversal of the myopathy may follow thyroid hormone replacement, although animals with severe neuromuscular signs may have slow or incomplete resolution of signs [142]. The few cases I have seen appear to have been primary myopathies, with no qualitative or quantitative (morphometric) evidence of peripheral nerve changes [134]. This is interesting given the fact that hypothyroid neuropathies comprise a significant proportion of cases seen in my peripheral nerve laboratory (see hypothyroid neuropathy). Some reports of dogs with hypothyroidism and unilateral forelimb lameness along with widespread electrodiagnostic changes in muscles (positive sharp waves, fibrillation potentials) that are not reflected clinically, may be examples of hypothyroid myopathy [143].

### **Hypotrophic Myopathy**

A subclinical myopathy has been reported in pectineus muscles of German Shepherd dogs that is characterized by a retardation in muscle fiber growth particularly of type 2 fibers [144]. It has been suggested that hypotrophy of the pectineus muscle may potentially influence the development of the coxofemoral joint; however, the relationship between pectineal myopathy and subsequent development of hip dysplasia has not been substantiated. Indeed, hip dysplasia can still develop in dogs in which the pectineus muscle has been exercised.

### **Immobilization Myopathy**

A syndrome characterized by pelvic limb hyperextension, generalized muscle atrophy in the affected limb, abducted gait, and a limited range of stifle joint range of motion has been reported in five dogs, four of which were immature [145]. Distal femoral fractures, of traumatic origin, were found in all dogs; four dogs were subjected to limb immobilization in extension for three to seven weeks. Lesions in muscle biopsies included fiber size variability associated with multifocal/diffuse presence of small atrophic fibers, increased prominence of subsarcolemmal nuclei, increased perimysial fibrosis and focal necrosis. These changes were most severe in the vastus lateralis, with less severe changes seen in the biceps femoris and gastrocnemius muscles. Histochemical and morphometric studies demonstrated a significant type 1 fiber atrophy and loss in the vastus lateralis muscles in the limbs with femoral fractures treated by hyperextension. The shortest time period between onset of fracture and the presence of type I fiber atrophy was seven weeks (there was no correlation between the extent of type 1 fiber atrophy and duration of limb immobilization). The pathogenesis of this condition, termed "stiff-stifle syndrome", is not well understood, although immobilization of muscle induces muscle atrophy and this change is especially influenced by the degree of stretch in which the muscle is held. In animals with limb immobilization in extension, the quadriceps muscle group, held in a shortened state, undergoes selective and progressive atrophy. Additionally, joint stiffness may be exacerbated by fibrous adhesions in and around the stifle joint while it is maintained in an extended position. A similar condition occurs in people [146-148]. Experimental studies indicate an increase in numbers of glucocorticoid receptors in immobilized muscles [88]. Prognosis is guarded, as all dogs in our study failed to show clinical improvement after removal of the immobilization device. Breakdown and removal of adhesions by surgical management may result in a return of function of the femorotibial joint. In experimental studies in dogs, a reversible type I fiber atrophy occurred in most restricted muscles and early type II fiber atrophy was seen in a few muscles after trauma and splinting [149]. Multifocal fiber necrosis was the only irreversible change seen after 3 weeks of splinting with or without concurrent muscle trauma. Relative fiber percentages did not change appreciably during splinting or recovery. In this study, the limited joint motion appeared to be related to shortening of the extensor mechanism of the femorotibial joint. Clinical signs similar to the stiff-stifle syndrome are seen in dogs with congenital limb contractures [150]. Interestingly, we did not observe muscle lesions in a dog with a proximal tibial fracture followed by a 3 week period of immobilization.

### **Ischemic Neuromyopathy**

This is a disorder that occurs not infrequently in cats caused by thromboemboli usually associated with cardiomyopathy [151]. While hypertrophic cardiomyopathy has now become the most important cardiac disorder in cats following the discovery of the role of taurine deficiency in dilated cardiomyopathy [152-155], in one review aortic thromboembolism reportedly occurred in approximately 50% of cats with hypertrophic cardiomyopathy, 25% of cats with dilated cardiomyopathy, and 25% of cats with restrictive cardiomyopathy [151]. It has also been seen in a small percentage of

cats with cardiomyopathy associated with excessive moderator bands [156]. In one report on 100 cats with distal aortic thromboembolism [157], the average age was 7.7 years, with the neutered male being overrepresented. Evidence of preexisting cardiac disease was found in 11% of the cases, with murmur or arrhythmia noted in > 50 % of the cases on presentation, and the most frequent underlying disease was hypertrophic feline cardiomyopathy. Cardiovascular disease (cardiomyopathy and thromboembolism) associated with taurine depletion was an unexpected finding in 3 of 6 healthy adult cats during a potassium - depletion study [158].

The cause of the disease and emboli formation in the heart are uncertain, although recent studies suggest a possible role for vitamin B12 and arginine in cardiomyopathy and arterial thromboembolism [159]. Predisposing factors to thrombus formation may include exposed vascular subendothelial tissue, abnormal circulation patterns and heightened platelet activity, and increased blood coagulability [151]. The origin of the embolus is a thrombus, an aggregate of fibrin and platelets attached to an endocardial surface, usually within the left atrium. An embolus breaks loose from the cardiac thrombus and occludes one or more branches of the aorta. The emboli may be carried to any site within the arterial circulation. The most common site of occlusion is the aortic trifurcation. Embolic occlusion at this site obstructs internal and external iliac arteries and the median sacral artery. Emboli which extend into the iliac arteries have been termed "saddle thrombi". A less common embolic site is the brachial artery [160]. Vasoactive substances released from embolic platelet products, such as serotonin, thromboxane A<sub>2</sub>, prostaglandins and 5-hydroxytryptamine may impair collateral circulation [161]. Cats of the Persian breed may be at risk for ischemic neuromyopathy [162], although this has been disputed [163].

Clinical signs are acute in onset and usually include pelvic limb pain during the first 24 hours, plantigrade stance, and paraparesis or paralysis. Signs may be unilateral or bilateral. Femoral pulse may be weak or absent, the cranial tibial and gastrocnemius muscles are firm and often painful, and the limb(s) are cool. Distal limb muscles below the stifle are particularly affected. Flexion and extension of both hip and stifle joints and the patellar reflex are usually present, although initially, limb(s) may be held rigidly extended because of ischemic muscle contracture [151]. Pain sensation to noxious stimuli is typically absent in the distal limbs. The nail bed of pelvic limbs is cyanotic. Left forelimb paralysis is seen with brachial artery embolization.

Electrodiagnostic studies reveal an absence of or markedly reduced evoked potentials from interosseous and cranial tibial muscles. Nerve conduction velocities are frequently reduced. Chest radiography may indicate cardiopulmonary disease (pulmonary edema, biventricular failure), and electrocardiographic/echocardiographic abnormalities are common (e.g., increased septal and/or left ventricular free wall thickness) [157,163]. Diagnosis of occlusive vascular disease can be confirmed from an aortogram. Pathologically, changes occur in skeletal muscle and peripheral nerve [164]. Lesions in peripheral nerves begin in the mid-thigh region, with the central fibers in a fascicle being more susceptible than peripheral fibers. The majority of fibers show changes of axonal degeneration, while others have evidence of paranodal/segmental demyelination. In skeletal muscle, ischemic myopathy characterized by focal necrosis, myophagia, internalized nuclei, and occasional mononuclear cell infiltrates, contributes to the clinical signs.

Improvement in nerve conduction velocities and evoked potentials correlates well with return of limb function. Femoral pulses frequently return within 1 to 2 weeks. At present there are no results that show that any treatment of the aortic thromboembolism produces a significantly better recovery than no therapy. Surgical embolectomy does not appear to be warranted; besides, cats with unstabilized cardiomyopathy are definite surgical risks. Use of thrombolytic agents to dissolve the emboli awaits clinical trials. For animals that are in pain, movement should be restricted. Morphine sulfate, at 0.1 mg/kg, subcutaneously, will produce analgesia (without excitement) for 4 hours [151]. This can be repeated every 4 to 6 hours for 2 days. In an attempt to prevent future episodes, affected cats should receive aspirin, at 25 mg/kg PO, every third day, for life. Aspirin inhibits platelet aggregation and preserves collateral circulation. While aspirin might prevent recurrences, it will have little effect on the underlying cardiomyopathy. It has been reported that there is no difference in survival time or rate of recurrence with warfarin vs. aspirin, and that low-dose aspirin (5 mg PO q3d) is an inexpensive option for thromboprophylaxis that seems to be as effective as high-dose aspirin (40 - 162 mg PO q 2 - 4 d) and warfarin [517]. Supportive care for initial cardiac decompensation includes administration of oxygen, diuretics, fluid therapy, glucocorticoids, and external heat [151].

Although the collateral circulation does return in the majority of cases with return of function to varying degrees (some cats with extensive limb necrosis do not recover; others retain dropped hocks) within 6 weeks to 6 months (an increase in nerve conduction studies and evoked potentials may correlate with return of limb function [164]), the long-term prognosis is guarded to poor because of the potential of further thromboembolism. Other potential complications are associated with reperfusion of ischemic tissues and include release of toxic factors such as lactic acid, potassium, and myocardial depressant factor [151]. Thus, the severity of the cardiac disease usually determines prognosis. Limb complications may include necrosis requiring amputation or wound management, and limb contracture [517]. In one retrospective study of idiopathic feline hypertrophic cardiomyopathy, analysis of survival revealed that all cats with thromboembolism were dead 6 months after diagnosis [163]. In another study involving cats with distal aortic thromboembolism, the average, long-term survival in the 37% of cases that survived the initial thromboembolic episode was approximately 12 months, while the remaining cases either died (28%) or were euthanized (35%) [157]. Long-term survival time is reportedly significantly shorter in cats with congestive heart failure during the initial episode [517]. Hypothermia has been associated with poor outcome [517].

Ischemic neuromyopathy secondary to aortic foreign body obstruction have occasionally been reported in cats [165,166].

In one case, in addition to muscle and nerve damage similar to that described above in thromboembolic disease, spinal cord infarction was present in lumbosacral spinal cord gray matter resulting in clinical signs of a lumbosacral syndrome (absent anal tone, bladder incontinence, megacolon, pelvic limb paresis, and flaccid analgesic tail) [165]. Removal of the foreign body by aortotomy was successful in another cat that recovered almost completely within one year after the surgery (external coaptation splints facilitated return of function of the pelvic limbs)[166]. Post-surgical therapy included heparin (100 U/kg IV q4h for 3 days), aspirin (25 mg/kg PO every 3 days for a total of 4 treatments), cefazolin (20 mg/kg IV q6h for 4 days), and methylprednisolone sodium succinate (20 mg/kg IV immediately after surgery and again 6 hours later).

Thromboembolic disease is not common in dogs but may be seen associated with hypercoagulable states, bacterial endocarditis, dirofilariasis, hyperadrenocorticism, neoplasia, cardiac disease (although thromboembolism secondary to cardiomyopathy has not been reported in dogs) [82,151,167-169]. Yet curiously, aortic thromboembolism in dogs has been reported infrequently [82,170-172]. In one report of 36 dogs with aortic thromboembolism, 4 had severe atherosclerosis associated with thyroid disease [170]. Thrombotic occlusion of the distal aorta and/or the iliac arteries in dogs results in signs of pelvic limb weakness, pain and collapse. Diagnosis is based on clinical signs, angiography and ultrasonography. In one report, dogs that survived the acute episode received aspirin in an attempt to prevent recurrence of thrombosis and all regained pelvic limb function [82]. For dogs that survived longer than one month after the acute episode, repeat thrombosis was uncommon. Aortic thromboembolism in dogs carries a more favorable prognosis than feline aortic thromboembolism.

A possible genetic predisposition to femoral artery occlusion occurs in Cavalier King Charles Spaniels [173]. The condition is usually subclinical due to sufficient collateral circulation (femoral pulse may be undetectable unilaterally or bilaterally).

### **Labrador Retriever Hereditary Myopathy**

A degenerative myopathy that is inherited as an autosomal recessive trait has been reported in Labrador Retriever dogs in the United States and United Kingdom, and has been seen in Continental Europe and Australia [174-180,520]. The condition has been called Labrador Retriever hereditary myopathy (LRHM), Labrador Retriever myopathy, type 2 muscle fiber deficiency and muscular dystrophy. The disorder affects male and female dogs and has been seen in animals with both black and yellow coat color. The age at onset and the severity of clinical signs may be variable. Some puppies have clinical signs at 6 to 8 weeks of age. In others, a later onset at 6 to 7 months has been observed. Cases of both early (8 weeks) and late (6 months) onset have been observed within the same litter. In typical cases, clinical signs become obvious at 3 to 4 months of age and include muscle weakness, abnormalities of gait and posture, and decreased exercise tolerance. Severely affected puppies may have a low head posture, with ventroflexion of the neck. The back is arched, and the gait is characterized by short, stilted strides in which the hind legs are often advanced simultaneously in a synchronous, bunny hopping fashion. Clinical signs become more accentuated as the animal tires, and, if encouraged to continue, the puppy may collapse forward with the head and neck to one side. There is no loss of consciousness or cyanosis. Exercise tolerance may be reduced to 20 yards in severely affected animals. Severe tetraparesis, inability to walk, hyporeflexia, and elevated serum CK levels have been seen in two 4 month old littermates [178]. However, mildly affected dogs may be presented because they seem to be "slow" puppies that are less playful than their littermates and less willing to exercise. These dogs may not collapse unless forcibly exercised, at speed, for several minutes. Rest results in some improvement, but the clinical signs rapidly recur on resumption of exercise. Joint posture is often abnormal, with affected dogs having carpal overextension, carpal valgus, splaying of the digits, and a "cow-hocked" stance. As the condition progresses, generalized atrophy of skeletal muscles develops. The proximal muscles of the limbs and the muscles of the head are particularly affected, but in milder cases, the atrophy may not be dramatic. Signs may be exacerbated by excitement or stress and particularly by exposure to cold weather. After exposure to cold, an affected dog may be unable to stand or to lift its head. Moving the animal to a warm kennel usually results in improvement within a few hours. A less common complication observed in adult dogs (some of whom have been pregnant) is the development of a transient megaesophagus. Other sporadic complications that have been observed include the presence of a luxating patella and clinical and radiographic evidence of degenerative joint disease in the hip of one affected dog that was obese. Affected dogs are bright and alert, although often poorly muscled when compared with their normal littermates. Temporal muscle atrophy is often a feature, but cranial nerve functions are otherwise normal. Muscle tone may be normal or reduced. There is no muscle pain on palpation nor dimpling on percussion. Severely affected puppies are obviously weak and may have difficulty wheelbarrowing or hopping, although in less affected puppies, postural testing may indicate no abnormalities. Proprioceptive function is normal, and no sensory deficits have been observed. Tendon reflexes are generally reduced or absent, even in mildly affected dogs with little muscle atrophy. There is no impairment of bladder function and no signs of autonomic nervous system dysfunction.

Serum CK levels may be within normal limits or moderately elevated. Levels may increase following exacerbation of signs after exposure to cold weather but do not reach the levels reported in other degenerative muscle diseases, such as the inherited muscular dystrophy described in Golden Retrievers (see muscular dystrophy). Other routine hematological and blood biochemical parameters are within normal limits. Motor nerve conduction velocities are within the normal

range in affected dogs, and there is no decremental response to repetitive nerve stimulation. On EMG examination, there frequently is spontaneous activity, particularly in the proximal limb muscles, musculature of the head, and the thoracolumbar paraspinal muscles. The most commonly recorded abnormalities are fibrillation potentials, positive sharp waves, and bizarre high-frequency discharges [181]. Myotonic-like discharges and fasciculation potentials are recorded infrequently. EMG changes may be less pronounced in mildly affected dogs and may be difficult to detect in very young dogs. Results of electrocardiographic examination of affected adults and puppies have indicated no cardiac involvement. Despite the abnormal joint posture seen in many affected dogs, there have been no abnormalities on radiography of hocks, carpi, and the vertebral column. In some cases, however, changes consistent with hip dysplasia have been present. A wide range of morphological features may be observed in muscle biopsies from affected dogs. The changes reported include small and large group atrophy, small fibers of both fiber types that tend to have a round rather than angular appearance, occasional fiber type grouping, large numbers of internal nuclei, disturbances in myofiber architecture, necrosis, regeneration, and replacement of muscle fibers with fat and fibrous tissue. Alterations in fiber type percentages are a common finding. In most muscles there is a reduction in the proportion of type 2 fibers (except for the cranial tibial muscle in which an increase in the percentage of type 2 fibers has been noted) [182]. These changes in fiber type proportions appear to become more accentuated as the disease progresses. No abnormalities have been found in brain, spinal cord, or peripheral nerves. Note that similar histological findings have been observed in clinically normal Labrador Retrievers closely related to those with LRHM [520]. It has been suggested that an additional gene or an environmental factor is responsible for expression of the subclinical form of the disease [520].

The underlying pathophysiological mechanisms involved in this disease are still unclear, although the myopathy has genetic, clinical, pathological, and histochemical similarities to the limb-girdle form of muscular dystrophy in people [183]. Myofiber dystrophin staining is normal. However, immunocytochemical and Western blot studies reveal that sarcoglycans, alpha-actinin, dysferlin, and calpain 3 are present in affected dogs [184]. These sarcolemmal and Z-disc (alpha-actinin) proteins have been incriminated in various limb-girdle muscular dystrophies in people [185-187]. Muscle biochemical studies indicate significantly elevated concentrations of sodium, calcium, zinc, copper, and chloride and reduced levels of potassium and magnesium in muscles from affected adult Labrador Retrievers [182]. There is a significant increase in the intracellular water and sodium levels and a concomitant reduction of intracellular potassium content [188]. In addition, a significant decrease in muscle-specific proteins has been identified in the biceps femoris muscle of affected dogs [189]. Also, lipid fluidity of erythrocyte membranes is significantly different in affected Labrador Retrievers [190]. Results of other studies have not supported the hypothesis of a possible vascular defect [191]. Diagnosis is based on signalment, clinical signs, and muscle biopsy data. Prognosis is generally favorable for longevity. In most cases, the clinical signs stabilize between 6 months and 1 year of age. There may be some improvement in ability to exercise, particularly in those dogs with the mildest signs. The atrophy of skeletal muscles persists, however, and although affected dogs may be acceptable house pets, they are not suitable for work. Owners of affected dogs should be warned that stress, including exposure to low temperatures, can result in a dramatic worsening of clinical signs, even in clinically stable adults. The life span of affected dogs does not appear to be directly affected by the condition, although the prognosis for dogs with megaesophagus should be more guarded because of the risk of developing inhalation pneumonia.

There is no definitive treatment for this condition, although various forms of medication have been used. Diazepam, given orally at a dose of 10 mg twice daily, may have some ameliorating effect. Diphenylhydantoin has little effect, and edrophonium chloride may worsen clinical signs. Anabolic steroids have apparently been beneficial in some cases; however, the evidence for this is anecdotal. Low muscle carnitine levels have been found in a few dogs tested suggesting that administration of L-carnitine (at 50 mg/kg PO bid) might be beneficial [192]. Because there is no way of detecting heterozygous carriers at this time, breeders should be advised against breeding from parents or siblings of affected puppies. Molecular studies are currently being undertaken at the Scott-Ritchey research Center, Auburn University College of Veterinary Medicine. There has been a recent preliminary report of a condition termed "canine centronuclear-like myopathy" in Labrador Retrievers in which onset, clinical signs, pathology (including centrally-placed myofiber nuclei) and histochemistry are virtually identical to those seen in LRHM [521]. The authors report that the gene for this condition (CNM gene) is localized on canine chromosome CFA2 and suggest that the disorder is a homologue of the human autosomal centronuclear myopathy. The relationship of this disorder to LRHM, if any, remains to be seen.

### **Limber Tail**

A condition colloquially referred to as "limber tail", "limp tail", and "cold tail" is familiar to people working with hunting dogs, primarily Pointers and Labrador Retrievers [193-198]. The typical case consists of an adult dog that suddenly develops a flaccid tail. The tail either hangs down from the tail base or is held out horizontally for several inches from the tail base and then hangs straight down or at some degree below horizontal. Initially, the hair on the dorsal aspect of the proximal tail may be raised and dogs may resent palpation of the area 3 - 4 inches from the tail base. Affected Pointers almost always have a history of prolonged cage transport, a hard workout the previous day, or exposure to cold or wet weather. Pain may be noted in acute stages of the condition. In cases where people are not familiar with this disease, other conditions such as a fracture, spinal cord disease, impacted anal glands, or prostatic disease have been incorrectly diagnosed. Results of a recent study [193] in 4 affected Pointers showed evidence of coccygeal muscle

damage, which included mild serum elevation of CK early after onset of clinical signs, needle electromyographic examination showing abnormal spontaneous discharges (e.g., positive sharp waves and/or fibrillation potentials) restricted to the coccygeal muscles several days after onset, and histopathologic evidence of muscle fiber damage (fiber size variation associated with multifocal fiber hypertrophy and scattered round/angular fibers many of which were basophilic, internal nuclei, fiber splitting, and mild fat infiltration, and in some instances, diffuse fiber atrophy). Specific muscle groups, namely the laterally positioned intertransversarius ventralis caudalis muscles, were affected most severely. Intramuscular nerves appeared normal. Infrared thermography revealed increased temperatures of the sacrococcygeal area and the entire tail in acute cases, indicative of reduced blood flow possibly associated with local edema, swelling and vascular stasis. Radionuclide perfusion imaging indicated uniform vascular perfusion over the lumbosacral area and tail of one affected dog, however, an area of increased radioactivity (indicative of increased vascularity or perfusion) was seen in the proximal tail caudal to the anus in another dog. No significant abnormalities were seen in the lumbosacral or coccygeal regions using imaging techniques (MRI, CT). The authors suggested the condition may be related to acute compartment syndrome (a condition in people associated with muscle ischemia, pain, pallor, pulselessness, paresthesia, and paralysis [199,200]) caused by tail injury, perhaps from damage associated with eccentric muscle contractions from tails being whipped from side to side. Treatment strategies include rest to allow healing of the muscle damage and short-term administration of anti-inflammatory drugs during the acute stages (anecdotal reports suggest that anti-inflammatory drugs administered within 24 hours of onset hasten recovery) [38]. Prevention is aimed at minimizing predisposing factors, including instituting regular training programs so as to avoid overexertion in unconditioned dogs, and regular stops with exercise when travelling long distances [38]. Prognosis is usually favorable with most dogs recovering spontaneously within a few days to weeks. Less than one half of affected dogs experience a recurrence.

### **Malignant Hyperthermia**

Malignant hyperthermia (MH) is a life-threatening hypermetabolic and contractile condition that is triggered in humans, pigs, dogs and cats by certain anesthetic agents (e.g., halothane and succinylcholine). The underlying defect in calcium (Ca) homeostasis occurs at the level of the skeletal muscle sarcoplasmic reticulum where there is hypersensitive and heightened ligand-gating of the Ca-release channel [201]. The Ca channel is readily opened by certain drugs, such as caffeine and halothane. Caffeine- or halothane-induced muscle contracture develops as a result of sustained increase in cytoplasmic Ca levels and subsequent activation of the actin-myosin contractile proteins. In addition, calcium uptake is reduced. The continuous contraction results in depletion of glycogen stores, hypoxemia, and accumulation of heat, hyperkalemia, lactic acid, and metabolic and respiratory acidosis. In people, as a consequence of severe muscle necrosis, CK levels may rise 100-fold and myoglobinuria and disseminated intravascular coagulation may occasionally occur, which may lead to renal failure [9]. Recent reports indicate that canine malignant hyperthermia is caused by a mutation in the gene encoding the skeletal muscle calcium release channel (RYR1) [23], similar to that found in pigs and humans. Malignant hyperthermia has been reported in various breeds of immature and mature dogs: St. Bernard, Border Collie, Labrador Retriever, Pointer, Spaniel, Greyhound and animals crossbred with Doberman Pinscher [202-207]. MH in some colony-bred dogs is inherited as an autosomal dominant trait [23,204]. Dogs susceptible to MH may be nervous and difficult to handle. Their muscles may be hypertrophic with greater than normal muscle tone and strength. Resting body temperature may be high normal or slightly above and serum CK and aspartate transaminase levels may be mildly elevated. While Greyhounds are often reported with MH, some studies indicate they may not be specifically MH susceptible [208]. MH has been reported only sporadically in cats [209].

Reports of MH in dogs and cats are most often associated with halothane anesthesia. It should be noted that this disorder does not always occur during the first exposure to halothane anesthesia. Clinical signs can include hyperthermia, tachycardia, tachypnea, severe limb rigidity, and trismus, followed by respiratory and cardiac arrest. In some animals, extreme trismus and generalized muscle rigidity occur immediately after death. Succinylcholine and enflurane, but not methoxyflurane, have also been implicated as triggers of MH in the dog. A MH-like episode was reported in a 5 year old Greyhound anesthetized with thiamylal sodium and also given lidocaine for premature ventricular contractions [210]. In another adult Greyhound, two episodes of malignant hyperthermia occurred at 20 and 44 hours post-surgery following anesthesia with fentanyl-droperidol and sodium pentobarbital [206].

Histopathologic features in skeletal muscle tend to be fairly non-specific and include fiber size variation, fiber hypertrophy, and increased numbers of internal nuclei in muscle cells [203]. Occasional perivascular infiltrates of lymphocytes with infrequent perimysial and epimysial neutrophils have also been noted [209]. In some patients, muscle biopsies are normal. Ultrastructurally, there may be loss of mitochondria, presence of moth-eaten fibers, cores, and Z-line streaming. Cardiac histomorphometric parameters are normal in MH-susceptible dogs [211].

Diagnosis of fulminating MH can be suggested by historical data relating to breed or colony susceptibility, and by development of characteristic clinical signs while under or following (see above) anesthesia. Signs may occur after 30 to 300 minutes of halothane exposure.

Prognosis is guarded. Removal of triggering agents and symptomatic treatment (total body cooling, corticosteroids, sodium bicarbonate, intravenous fluids) usually are ineffectual in reversing MH episodes, although hyperventilation with 100% oxygen, stomach lavage with iced water, body surface cooling, and IV administration of cold isotonic saline

solution was successful in one report [202]. Dantrolene is the drug of choice for treating affected animals [212]. It can prevent a malignant hyperthermia crisis or reverse anesthetic-induced MH if given early in the development of the syndrome [213]. A recommended intravenous dosage is 3 to 5 mg/kg. Injectable dantrolene may also be prepared from an oral preparation [214].

In instances where MH is suspected, susceptible animals can safely undergo anesthesia if triggering agents are avoided. Screening tests for animals susceptible to MH include caffeine/halothane-contraction tests (CCT), erythrocyte osmotic fragility test (EOFT), lymphocyte Ca test, and biochemical tests for defective Ca-transport in sarcoplasmic reticulum isolated from skeletal muscle [203,215,216]. Several reports have noted that the initial sign of a MH episode was a rapid increase in end tidal partial pressure of carbon dioxide before any increase in rectal temperature or muscle tone [204,213].

It is now established that the Ca channel may also be triggered by stressors such as excitement, fighting for dominance, and sudden increase in ambient temperature in pigs, and by exercise, in dogs. This exercise-induced hyperthermia has been termed "canine stress syndrome" [203,217] and has been reported in several breeds including an English Springer Spaniel and a Greyhound [218,219]. In susceptible dogs, the stress of moderate exercise can cause a reversible MH-like syndrome characterized by hyperthermia (e.g., 42°C), muscle cramping, dyspnea (labored stertorous breathing), panting (e.g., respiratory rate > 200 breaths/minute), hemoconcentration, hyperlactemia, respiratory alkalosis, and raised levels of muscle enzymes. Similar findings have been reported in Labrador Retrievers following strenuous exercise [220]. Dogs with the exercise-induced hyperthermia are clinically normal but reportedly have a hyperactive temperament [218,219]. Absence of myoglobinuria rules out a diagnosis of exertional rhabdomyolysis. Hypercontracted myofibers have been observed in muscle biopsies [219]. Recovery can be relatively rapid (e.g., within 30 minutes of rest) and this condition may represent "mild aborted malignant hyperthermia" [219]. A suggested diagnostic protocol for animals with canine-stress syndrome includes exercise/challenge testing, EOFT, and serum CK levels [219]. In susceptible animals, CCT and EOFT are not always positive [218]. The halothane-challenge test is likely risk prohibitive. Note that in dogs with exercise-induced hyperthermia, administration of dantrolene prior to exercise may not prevent the stress syndrome occurring [219].

### **Megaesophagus**

This condition refers to esophageal dilatation with absence of effective esophageal peristalsis. Megaesophagus has been termed esophageal achalasia, esophageal dilatation, esophageal hypomotility, and esophageal neuromuscular disease. Both congenital idiopathic (CIM) and acquired forms of megaesophagus occur. Congenital megaesophagus has been reported in Great Danes, German Shepherds, Irish Setters, Newfoundlands, Shar Peis, and Greyhounds. The condition occurs as an inherited disease in Wire-Haired Fox Terriers (autosomal recessive) and Miniature Schnauzers (autosomal dominant or 60% penetrance autosomal recessive). A suspected hereditary form has been reported in Bouvier des Flandres dogs (see Bouvier des Flandres myopathy) [2]. Idiopathic megaesophagus is also reported in cats [221-223], with a predisposition noted in Siamese and Siamese-related breeds [222]. The congenital form is usually apparent in animals around the time of weaning. Less commonly, adult-onset idiopathic megaesophagus may be detected [224]. Readers should refer to other texts for more information on megaesophagus associated with obstructive esophageal disease such as neoplasia, granulomas, vascular rings, strictures, periesophageal masses, and foreign bodies.

Acquired megaesophagus may occur in dogs or cats at any age, although in one study, older (mean = 8 years), heavier dogs were at risk, including German Shepherds, Golden Retrievers and Irish Setters [225]. In many cases, the cause is unknown; however, the condition has been observed in association with certain systemic neuromuscular disorders such as myasthenia gravis, botulism, hypoadrenocorticism (associated with glucocorticoid deficiency with or without concurrent mineralocorticoid deficiency), polymyositis, dermatomyositis, myotonic myopathy, nemaline myopathy, polyradiculoneuritis, distemper, giant axonal neuropathy (German Shepherds), tick paralysis, lead toxicosis, thallium toxicosis, canine and feline muscular dystrophies and dystrophy-like conditions, laryngeal paralysis-polyneuropathy complex, dysautonomia, glycogen storage disorders, feline mannosidosis, sensory ganglioradiculitis, and spinal muscular atrophy [136,225-231]. In acquired myasthenia gravis in dogs, megaesophagus may be the only clinical sign. It has also been reported sporadically in canine pituitary dwarfs, dogs with tetanus, and Labrador Retriever puppies with familial reflex myoclonus [227]. In one report, megaesophagus was noted in English Springer Spaniels with a polysystemic disorder comprising dyserythropoiesis, polymyopathy, and cardiac disease [232]. Megaesophagus may also occur with bilateral vagal nerve damage due to surgery, trauma, or neoplasia as well as with various brainstem lesions - neoplasia, distemper encephalitis, granulomatous meningitis/meningoencephalomyelitis, trauma, and infarction [233]. It has also been observed in dogs secondary to tiger snake envenomation [536]. It has been stated that the relationship between hypothyroidism and megaesophagus has yet to be established [225,539]. In one report, megaesophagus was found in 5 dogs with hypothyroidism and myasthenia gravis [136].

The pathogenesis remains elusive. Megaesophagus may result from lesions involving the esophageal muscle, or afferent/efferent pathways controlling esophageal motility [226,234]. Afferent pathways include esophageal sensory

receptors, afferent fibers in the vagus nerve and its branches (e.g., cranial laryngeal nerve), and the solitary tract/nucleus complex. The efferent limb of the reflex comprises the vagus nerves (including special visceral efferent axons from the nucleus ambiguus and general visceral efferent fibers from the parasympathetic vagal nucleus), neuromuscular junction, and esophageal muscle (primarily skeletal, with less involvement of smooth muscle) [234,235]. Electrolytic lesions of the nucleus ambiguus in dogs and of the parasympathetic nucleus of the vagus in cats produce esophageal dysfunction similar to the clinical syndrome [236]. A reduction of the normal number of neuronal cell bodies in the nucleus ambiguus has been recorded in clinically affected dogs, but not in affected cats [237,238]. These neuroanatomical differences between dogs and cats with megaesophagus probably relate to differences in proportion of striated and smooth esophageal muscle between the two species [226,235]. In one study in 12 week old Chinese Shar Peis with CIM, no histological lesions were found in the nucleus ambiguus or parasympathetic nucleus of the vagus, or in ganglion cells of the myenteric plexus [239]. CIM appears to be associated with loss of peristaltic function in the esophagus due to developmental immaturity of innervation and/or musculature [240]. Based upon studies of upper and lower esophageal responses to intraesophageal balloon distension, CIM was considered to be at least partly due to a faulty afferent component of the reflex neural pathway that controls swallowing [241]. Seemingly consistent with this finding, more recent studies on dogs with CIM showed no electrophysiological evidence for segmental demyelination or axonal degeneration in cervical vagal motor fibres innervating striated muscle of the thoracic esophagus portion and no EMG abnormalities indicative of esophageal muscle denervation or primary myopathy [242]. Additionally, demonstration of a normal Hering-Breuer lung inflation reflex is consistent with an organ specific, selective vagal afferent dysfunction in dogs with CIM [538]. Note that few cases of megaesophagus appear to be related to disturbances of gastroesophageal sphincter function [226]. In one study, resting caudal esophageal sphincter pressure was similar in clinically normal dogs and in dogs with congenital or acquired idiopathic megaesophagus [243].

Clinically, megaesophagus is characterized by postprandial regurgitation of undigested food, with radiographic evidence of megaesophagus, usually to the level of the diaphragm. Abnormal esophageal motility may be demonstrated by contrast radiography/fluoroscopy. In some dogs, respiratory signs such as cough, dyspnea and/or abnormal secretions may be the only signs observed.

Prognosis of congenital megaesophagus in young dogs is guarded. Some animals appear normal by the time they mature, based on radiographic, manometric, and clinical examination, while others show no clinical improvement with time.

Acquired, idiopathic megaesophagus generally has a poor prognosis for recovery [226], although transient megaesophagus followed by spontaneous recovery has been reported occasionally in dogs [178,224]. The prognosis for secondary megaesophagus varies with the underlying cause, for example, cats with megaesophagus and dysautonomia have a poor prognosis, while clinical improvement has been noted in dogs following treatment of the primary disease process, e.g., myasthenia gravis, hypoadrenocorticism, hypothyroidism, botulism, tetanus, and lead poisoning [226,231,244-246,537]. Cachexia becomes an important complication and death is a common consequence of inhalation pneumonia. Recommended management includes elevated feeding and/or gastrostomy tube feeding of high caloric diets [227,240]. Surgical treatment remains controversial. Pharmacological management, using drugs that relax the gastroesophageal sphincter or increase strength of esophageal contractions, has been disappointing [226], although sildenafil, a phosphodiesterase-5 inhibitor, is reported to have profound effects on esophageal motility in cats by modifying propagation and amplitude of esophageal contractions [247]. Nifedipine, a calcium channel blocker, resulted in temporary clinical improvement (2 months) in an adult German Shepherd with megaesophagus [248].

### **Mitochondrial Myopathies**

A myopathy has been reported in young Clumber and Sussex Spaniel puppies (male and female) in which clinical signs are usually seen with the introduction of lead training - about 3 months of age [249-253]. Animals tire easily, pull back on the leash, and collapse in sternal recumbency. Animals attempt to rise only after 10 to 15 minutes. During this time, excessive panting and tachycardia are noted. Animals appear thirsty and remain depressed for about an hour after each episode. Tensilon testing for myasthenia gravis is normal. Serum CK levels, along with EMG studies and nerve conduction velocities are normal [253]. Blood biochemical studies reveal a metabolic acidosis (nonhypoxic) in arterial blood samples due to elevated levels in lactate and pyruvate (resting levels are higher than normal and both increase dramatically above the levels expected following exercise), presumably leading to clinical weakness and muscle cramping. This metabolic disorder is believed to be associated with abnormal mitochondrial function. Biochemical studies showed that muscle mitochondria were unable to oxidize pyruvate (via the tricarboxylic acid cycle/Krebs cycle) due to a deficiency of pyruvate dehydrogenase (PDH) [249,251]. Recent studies have confirmed PDH deficiency in cultured fibroblasts from one affected Clumber Spaniel [253]. In this report, lactic acidemia with a lactate to pyruvate ratio < 10 was considered diagnostic for PDH deficiency. The etiology remains unknown, although the condition appears to be inherited (note that interbreeding between Clumber and Sussex Spaniels has occurred in the past). Treatment should be aimed at reversing the acidosis. More recently, a suggested treatment protocol includes a high fat and low carbohydrate dietary regimen, in conjunction with L-carnitine (50 mg/kg PO bid) and thiamine (100 mg daily) may improve exercise tolerance [253]. Prognosis appears guarded as dogs may die suddenly following exercise from cardiac arrest (presumably related to the metabolic acidosis).

A similar condition has been reported in two male Old English Sheepdog littermates (presented at 1 year of age and 2.5 -



years of age, respectively) with a history of clumsiness since 3 months of age [254]. Other signs included reluctance to play rigorously, and progressive exercise intolerance. Muscle biopsy data revealed scattered myonecrosis, ragged red fibers characterized by reddish-purple subsarcolemmal stain using modified Gomori's staining and dark blue subsarcolemmal deposits using the oxidative stain NADH-TR, empty sarcolemmal tubes, fibrosis, vacuolated fibers, and marked increase in numbers of internalized nuclei. Ultrastructural findings included scattered myofibrillar disruption, increased numbers of mitochondria, and increased myofibrillar glycogen. Electromyographic studies revealed increased insertional activity and complex repetitive discharges. Nerve conduction velocities were normal. Arterial blood analysis immediately after exercise showed a high anion gap metabolic acidosis associated with lactic acidosis and increased pyruvate levels, elevated lactate/pyruvate ratio, along with dramatic increase in serum CK, alanine aminotransferase, and aspartate aminotransferase activity. A subsequent biochemical study using fibroblasts and skeletal muscle from one of the affected dogs demonstrated a partial deficiency in cytochrome oxidase [255], suggesting that the exercise intolerance and elevated lactic acidosis resulted from impaired mitochondrial oxidative phosphorylation and reduced pyruvate usage. In skeletal muscle from the affected dog, reduced activity of two additional mitochondrial inner membrane enzymes (i.e., ATPase and NADH-ferricyanide reductase) was also found. Empirical treatment with vitamin C (at 10 mg/kg, daily), a drug considered to be useful in people with mitochondrial myopathy caused by complex III deficiency, had little effect in either dog.

More recently, similar clinical and pathological findings were reported in a 4 month old Jack Russell Terrier [256]. In this dog, exercise intolerance was progressive so that by 10 months of age, it could walk for only about 30 meters before collapsing. The dog was able to resume walking after a short rest (30 seconds). The muscle changes were worse at 10 months of age (increased numbers of ragged red fibers and increased fiber size variation associated with marked muscle fiber atrophy). While serum CK values were slightly increased, serum biochemical studies revealed a lactic acidosis before and after feeding, along with increased fasting level of pyruvate and a marked increase in the post - feeding lactate/pyruvate ratio (the pyruvate levels decreased to normal range after feeding). While mitochondria in this dog appear to be structurally normal, the authors regarded the blood biochemical findings to be consistent with a defect in the electron transport involved in oxidative phosphorylation, or in the enzyme pyruvate decarboxylase. Electrophysiological studies (nerve conduction velocities, EMG) in this dog were normal.

Exercise intolerance leading to ataxia and collapse within 15 minutes of strenuous activities is encountered in some working young-adult Labrador Retrievers [257] suggesting possible abnormal muscle oxidative metabolism. In a controlled study using healthy Labrador Retrievers, only brief periods of strenuous exercise were required to produce a marked increase in rectal temperatures, significant increase in arterial blood pH and oxygen partial pressure, significant decrease in arterial blood bicarbonate levels and carbon dioxide partial pressure, and marked increase in plasma lactate and pyruvate levels (the lactate/pyruvate ratio, however, remained normal) [220]. In this study, the metabolic acidosis were unassociated with clinical weakness or collapse. Similar metabolic changes have been noted in healthy racing Greyhounds [258-260]. The condition in the Labradors may be another example of exercise-induced hyperthermia (see Canine Stress Syndrome).

A lipid storage myopathy characterized by abnormal accumulations of lipid droplets (using lipid stains such as oil red O or Sudan black), localized predominantly in type 1 fibers, have been reported in male and female dogs of various breeds and ages with signs of myalgia, weakness, and muscle atrophy [261,262]. The occurrence of lactic acidemia, hyperalaninemia, lactic and pyruvic aciduria, variably increased urinary excretion of carnitine esters, and muscle carnitine deficiency suggested a metabolic block in mitochondrial oxidative metabolism. Recommended treatment for affected dogs includes L-carnitine (50 mg/kg, PO bid), coenzyme Q (100 mg PO daily), and riboflavin (100 mg PO daily) [262].

Note that mitochondrial dysfunction is considered to play a role in other myopathies, including hypothyroid myopathy and hyperadrenocortical (Cushing's) myopathy. Mitochondrial abnormalities (ultrastructural and abnormal biochemical respiration characteristics) were found in Irish Terrier puppies with possible X-linked inherited myopathy characterized by stiff gait, lumbar kyphosis, and dysphagia [263] and in older Golden Retrievers with muscular dystrophy [264] (see muscular dystrophy). Abnormal mitochondrial within neuronal perikarya and axons are a feature of mitochondrial encephalomyelopathy in dogs [265]. In people, mitochondrial myopathies are a complex and heterogeneous group seen in most diseases of oxidative phosphorylation [266]. The mitochondrial abnormalities are due to defects in the respiratory chain enzymes associated with mitochondrial DNA deletions [7]. Ultrastructural abnormalities in mitochondria may involve the number, size, or shape of mitochondria, and there may be changes in the patterns of the cristae and/or presence of crystalline or osmiophilic inclusions [120].

### **Muscular Dystrophy**

The muscular dystrophies are hereditary, degenerative dystrophinopathies and disorders of dystrophin-associated proteins. Dystrophinopathies are those muscular dystrophies in which there is a defect in the dystrophin gene (the cause of Duchene muscular dystrophy) [4]. Dystrophin binds to a complex of proteins and glycoproteins called dystrophin-associated proteins and dystrophin-associated glycoproteins. Muscle dystrophin occurs on the plasma membrane surface in skeletal muscle fibers, on plasma membrane and transverse tubule surfaces of cardiac muscles, and on smooth muscle

membranes. This membrane-associated protein is thought to help maintain membrane integrity. Dystrophin is a member of the spectrin superfamily of proteins. Dystrophin itself is closely related to three proteins that constitute a family of dystrophin-related proteins (DRP): utrophin, DRP2, and dystrobrevin [267]. There are several subcomplexes that form the glycoprotein complex involved with dystrophin [4,268]:

- a. The dystroglycan complex that consists of  $\alpha$ - and  $\beta$ - dystroglycans and forms the dystrophin-axis. The basal membrane of each muscle fiber contains several components including laminin, a subunit of which, merosin (also called laminin  $\alpha$ 2), is bound to  $\alpha$ - dystroglycan, which binds to the cysteine-rich and carboxyl-terminus domains of dystrophin. Merosin is also found in the basement membrane of Schwann cells of peripheral nerves (see congenital muscular dystrophy, below). The N-terminus domain of dystrophin is bound to actin filaments forming the cytoskeleton of the subsarcolemma. The dystrophin homologue, utrophin, is believed to bind to actin and the dystroglycan complex.
- b. The sarcoglycan complex that appears to be fixed to dystrophin axis in skeletal and cardiac muscles. There are four of these transmembrane glycoproteins:  $\alpha$ -sarcoglycan (also called 50DAG, A2, and adhalin),  $\beta$ -sarcoglycan (43DAG, A3b),  $\gamma$ -sarcoglycan (35DAG, A4), and  $\delta$ -sarcoglycan.
- c. The syntrophin complex  $\alpha$ ,  $\beta$ 1, and  $\beta$ 2 that binds to the distal part of the carboxy-terminal domain of dystrophin.

Perturbations in these proteins and glycoproteins result in several types of muscular dystrophy in people, as well as in dogs and cats.

### **Canine Muscular Dystrophy -**

Dystrophinopathies as exemplified by Golden Retriever muscular dystrophy have received considerable comparative interest because of their similarities to Duchenne muscular dystrophy (DMD) in people [269-272]. Molecular biology studies have shown that the Golden Retriever canine model is genetically homologous to DMD and its molecular basis has been described [273]. This degenerative myopathy in dogs, which has received the most attention of the canine "models" of human disease so far, has an X-linked inheritance (in which the disease is expressed in males and carried by females) and has been termed canine X-linked muscular dystrophy (CXMD). The genetic symbol *xmd* was proposed for this canine mutation [272]. Mutations in the DMD gene lead to disturbances in dystrophin expression, and this protein also is lacking in skeletal and cardiac muscle of affected dogs. Dystrophic muscle has also been shown to exhibit abnormal sarcolemmal expression of utrophin [274], but not of laminin [275]. Histopathological studies of skeletal muscle from affected Golden Retrievers reveal pronounced fiber size variation associated with atrophy and hypertrophy, endomysial and perimysial fibrosis, internalization of nuclei, marked hypercontraction, and segmental necrosis of muscle fibers with phagocytosis and regeneration (basophilic fibers), and increased levels of intracytoplasmic calcium [264,271]. Fibrosis may be mediated by fibrogenic cytokines, particularly transforming growth factor-beta1 [528]. Differential skeletal muscle involvement has been noted [276,277] while studies of postnatal muscle changes have shown that muscle damage occurs before completion of muscle maturation in dystrophic dogs, that necrosis and hypercontraction appear stable in adults but fiber regeneration declines, and that muscle fibrosis does not increase with age [278,527]. In CXMD dogs, there is a selective loss of fibers expressing fast myosin and persistence of immature developmental fibers [279]. Histochemical studies indicate a predominance of type I fibers in many muscles, and occasional fiber type grouping [264]. Ultrastructurally, there is dilatation of the sarcoplasmic reticulum, focal subsarcolemmal areas of degeneration, Z-band streaming and duplication, mitochondrial accumulation, and presence of nemaline rods (especially in older dogs) [264]. No abnormalities have been found in the central or peripheral nervous systems [276].

Clinical signs are first observed in affected male dogs from 6 to 9 weeks of age. These include stunting, weakness and gait abnormalities (e.g., stiff, stilted shuffling gait with abduction of elbows and bunny hopping in pelvic limbs), exercise intolerance, marked muscle atrophy of temporal, truncal, and limb muscles, fibrosis, and contractures by 6 months of age (semimembranosus and semitendinosus muscles may be hypertrophied). Other signs may include plantigrade stance, inability to fully open the jaw, progressive enlargement of the base of the tongue, signs of pharyngeal and esophageal dysfunction and excessive salivation, and weak bark. Skeletal deformities including variable lumbar kyphosis that may develop into lordosis by 1 year of age and curvature of the costal arch may also be seen, along with various muscle/limb conjectures [280,281]. Spinal reflexes may be diminished later in the disease. Clinical signs slowly progress during the first 6 months of life and then tend to stabilize [280]. Signs of inhalation pneumonia and congestive heart failure have been noted in older dogs and a lethal neonatal form has been recognized in some puppies [280].

Serum CK levels are markedly elevated and affected puppies can be identified by 1 week of age. CK levels reportedly peak at 6 to 8 weeks of age, just before onset of overt clinical signs [280]. After this time, CK levels plateau at approximately 100 times normal values. Serum CK levels do not show a clear correlation with clinical severity. Serum levels of muscle enzymes (CK and aspartate aminotransferase), as well as alanine aminotransferase activity, are increased after exercise [282], suggesting that in the absence of dystrophin, exercise-induced muscle injury may play a role in the dystrophic process [283]. Electrodiagnostic testing reveals pseudomyotonic discharges, especially in dogs over 10 weeks of age. Myotonic discharges may also be present but are less frequent. Positive sharp waves and

fibrillation potentials are not commonly noted. Flash electroretinographic abnormalities have been recently detected [284,529] that suggest a dysfunction in the rod signaling pathway. Prognosis is guarded to poor. At present, there is no effective treatment; however, potential strategies for gene therapy (including chimeraplast-mediated gene repair for dystrophin mutations) and bone marrow transplantation are being pursued at several institutions with variable success [267,285-288,526,530]. Treatment by nitric oxide donors (argenine and molsidomine) failed to modify the evolution of the disease in one study [523]. Molecular testing now provides rapid, accurate diagnosis of carrier and affected Golden Retrievers [289,290].

Females with the X-linked muscular dystrophy (produced from carrier female x dystrophic male breedings) manifest milder clinical signs compared to the males, but with similar CK levels and comparable histological lesions [264,281]. Results of breeding studies indicate that obligate female carriers of CXMD usually have no clinical evidence of disease although CK levels may be mildly elevated [280]. In skeletal muscle of carrier animals, dystrophin is expressed in a mosaic pattern with normal dystrophin-staining fibers muscle interspersed with severely affected fascicles and negatively-staining fibers, but as animals mature, dystrophin staining becomes more homogeneous and the number of negative-staining fibers declines [291]. In a recent developmental study, calcium- and albumin- positive fibers observed in carrier dogs, always expressed dystrophin abnormally [278], while utrophin was absent from muscle fiber surfaces in 2 day old animals, present between 15 and 30 days, and disappeared by 60 days [279]. Variable loss of dystrophin, dystrophin-associated proteins, or laminin  $\alpha 2$  deficiency has also been identified in female purebred and mixed-breed dogs in whom variable clinical signs were seen (including generalized weakness, exercise intolerance, muscle hypertrophy/atrophy, and limb deformities) along with variable CK levels (ranging from normal to high values) [292]. Histological changes included fiber size variability, degeneration/regeneration, and fibrosis.

Similar muscular dystrophies/dystrophinopathies have been reported in several canine breeds, including Rottweiler [293], German Shorthaired Pointer [294], Irish Terrier [295], Belgian Groenendaeler Shepherds [296], Samoyed [297], Miniature Schnauzer [298], Brittany Spaniel [299], Rat Terrier [300], and Labrador Retrievers [301,522]. We have seen similar pathological findings in a 4.5 month old, male, Welsh Corgi presented with stiffness, apparent muscle enlargement, and extremely high CK levels. Electromyography revealed diffuse, pseudomyotonic, bizarre high-frequency discharges in skeletal muscles. Prominent muscle changes were characterized by moderate/pronounced fiber size variation associated with atrophic (round, some angular) and hypertrophic fibers, scattered as well as in groups, multifocal necrosis, macrophage infiltration (positive acid phosphatase staining), multifocal fibers with internal nuclei, multifocal mineralization, fiber splitting, basophilia, and fibrosis. Histochemical staining showed involvement of both type 1 and type 2 fibers, although there appeared to be a type 2 fiber loss in some fascicles. There was also fiber type grouping. Immunocytochemical staining revealed an absence of dystrophin staining in myofiber sarcolemmal membranes. Spectrin staining was normal. An attenuated form of canine dystrophinopathy has also been reported in Japanese Spitz dogs in which staining was absent against the rod domain of dystrophin but not against the carboxy terminus, suggesting possible similarities to Becker's muscular dystrophy in people [302]. Labrador Retriever Hereditary Myopathy has genetic, clinical, pathological, and histochemical similarities to the limb-girdle form of muscular dystrophy in people, although a recent study [184] demonstrated that the canine disease was not due to a deficiency of alpha-actinin (a Z-disc protein that may be implicated in some forms of autosomal dominant limb-girdle muscular dystrophy in people), or any of the known autosomal recessive limb-girdle muscular dystrophy proteins identified in people, namely the sarcoglycans, dysferlin and calpain 3 [187]. A muscular dystrophic-like condition has also been reported in Bouvier des Flandres (see Familial Dysphagia) and in three related young English Springer Spaniel dogs with regurgitation from an early age [232] associated with slowly progressive temporal muscle atrophy with partial trismus, and generalized skeletal muscle atrophy. All dogs exhibited moderate dyserythropoietic anemia, polymyopathy (histological evidence of muscle fiber size variation and internalized nuclei without regeneration/inflammation) with megaesophagus, and varying degrees of cardiomegaly. The cause of this condition was not determined. In the English Springer Spaniels, EMG changes (fibrillation potentials) were patchy and there was no increase in serum CK levels.

Distal myopathies are a form of muscular dystrophy that occur rarely in people and are characterized by progressive muscular weakness and atrophy that starts in the hands or feet. Several types have been identified: late adult onset type 1 (autosomal dominant); late adult onset type 2 (autosomal dominant); early adult onset type 1 (autosomal recessive); early adult onset type 2 (autosomal recessive); and early adult onset type 3 [303]. Dysferlin, a sarcolemmal-associated protein, is absent in the early adult onset type 2 form (Miyoshi myopathy) although dystrophin and other dystrophin-associated proteins are normal in these patients [304]. Serum CK levels may be very high while nerve conductions are normal. A distal myopathy (termed juvenile-onset distal myopathy) has recently been reported in young Rottweilers (male and female) from three different litters in California (2 of the puppies were littermates) presented for decreased activity and various postural abnormalities, including plantigrade and palmigrade stance and splayed forepaw digits [305]. These clinical signs were seen in some puppies as early as 3 weeks of age. Neurological examination was normal. EMG studies revealed rare fibrillation potentials and positive sharp waves. While motor nerve conduction velocities were normal, compound muscle action potentials from the interosseous muscles were decreased. Serum CK levels were normal or

mildly increased. Histopathologic changes (more prominent in distal muscles) included myofiber atrophy with mild myonecrosis, endomysial fibrosis and replacement of muscle with fatty tissue. While plasma and muscle carnitine concentrations (total and free) were low in most puppies, the significance of this finding is uncertain but may be related to the degenerative process (metabolic testing did not reveal abnormalities in any intermediary metabolites). Dystrophin immunocytochemistry was normal. The condition in these dogs is considered to be inherited.

### **Feline Muscular Dystrophy -**

Muscular dystrophy-like disorders in cats have been reported in the Netherlands, Germany, and the US [306-309]. To date, all cats have been male, suggesting an X-linked inheritance. Clinical signs may be first seen in cats about 5 to 6 months of age and include generalized skeletal muscle hypertrophy, excessive salivation, reduced exercise tolerance, stiff gait and bunny-hopping when running, difficulty in jumping, adducted hocks, cervical rigidity, vomiting/regurgitation, and partial protrusion of the tongue. Multifocal lingual calcification (submucosal), hepatosplenomegaly, and megaesophagus have been noted in some cats [308]. Based on the clinical features, including the extensive muscle hypertrophy, the term "hypertrophic feline muscular dystrophy" has been proposed for this condition [308]. Serum CK levels may be markedly increased, often accompanied by variably elevated levels of aspartate aminotransferase and alanine aminotransferase. Atrial and ventricular dilatation, left ventricular wall thickening, and papillary muscle hypertrophy have been detected in echocardiographic studies. Notching of R waves has been noted with electrocardiographic testing. Electromyographic studies of skeletal muscles reveal bizarre high frequency discharges (also called complex repetitive discharges), sometimes interspersed with positive sharp waves [309,310]. Motor nerve conduction velocities are normal. Necropsy examination has shown severe hypertrophy of the diaphragmatic musculature, and enlargement of muscles of the tongue and larynx. Pathological findings are similar to those described for dystrophic dogs and include muscle fiber hypertrophy (involving both type 1 and type 2 fibers), fiber splitting, accumulation of calcium deposits within muscle, myonecrosis and phagocytosis (mononuclear cell infiltrates may be seen), hypercontracted fibers, numerous internalized nuclei, and occasional fiber type grouping. Aging studies have shown a significant decrease in the number of type 2A myofibers and increase in numbers of type 2X fibers in younger dystrophin-deficient cats [311], with an apparent loss of type 1 fibers in older cats [312]. Endomysial or perimysial fibrosis is not a feature in axial or appendicular muscles. Immunoblotting and immunofluorescent studies have shown marked dystrophin deficiency in skeletal muscles [307-309], although, a small percentage of fibers may stain positive [311]. Molecular studies have demonstrated deletion of the dystrophin muscle promoter in affected cats [313]. No histological lesions are seen in carrier females despite presence of a mosaic staining pattern for dystrophin in skeletal muscle (irregular staining in most myofibers or absent staining in rare fibers) [311]. Mineralization, fibrosis, and myodegeneration have been seen in cardiac muscle of some affected cats. Ultrastructural changes in skeletal muscle include distention of the sarcoplasmic reticulum and the T system, swollen mitochondria, and Z-band streaming. Prognosis is guarded in cats because of the development of diaphragmatic and lingual hypertrophy which potentially leads to megaesophagus, insufficient water intake, dehydration, hyperosmolar syndrome (see hypernatremia), and acute renal failure [308]. Another potential complication is rhabdomyolysis, possibly associated with increased sensitivity of the dystrophin-deficient sarcolemmal membrane to volatile anaesthetic agents, stress, or intense muscular activity. In one report, 3 dystrophin-deficient cats developed peracute, lethal rhabdomyolysis following either isoflurane anesthesia or manual restraint for a procedure) [312]. Serum chemistries revealed severe hyperkalemia, hyperphosphatemia, hypocalcemia, massive increases in CK, aspartate aminotransferase, and alanine aminotransferase concentrations, and high ion gap metabolic acidosis. Skeletal muscle changes included severe acute hyaline necrosis and endomysial edema without infiltration of inflammatory cells.

**Congenital Muscular Dystrophy** - A novel muscular dystrophy has recently been reported in cats associated with deficiency of merosin (laminin  $\alpha 2$ ) [314]. Laminins are large glycoproteins found in the basement membrane of a variety of tissues, including skeletal muscle fibers and Schwann cells of peripheral nerves. Clinical signs in the cats beginning around 6 months of age included progressive muscle weakness, muscle atrophy, and extraordinary muscle contractures resulting in rigidity and extension of the pelvic limbs in one cat. The second cat was non-ambulatory and hypotonic/hyporeflexive in all limbs. Serum CK levels were markedly elevated. Histological muscle changes were characterized by marked endomysial fibrosis, myofiber necrosis, variability of fiber size, and perimysial lipid accumulation. In both cats, immunohistochemical labeling showed complete absence or marked reduction in staining against laminin  $\alpha 2$ . However, staining for dystrophin and all the components of the dystrophin-associated glycoprotein complex were present and normal. In one cat studied, motor nerve conduction velocity was decreased, and demyelination and vacuolar Schwann cell degeneration were observed in peripheral nerves. No abnormalities were seen in the CNS and there was no evidence of cardiomyopathy. The disease was considered similar to primary or secondary merosin (laminin  $\alpha 2$ )-deficient congenital muscular dystrophy in people.

### **Myositis**

The incidence of myositis appears to be increasing in dogs and cats. Although several forms of myositis have been described in animals, a precise classification has not been established at this time. In this section, the different types of

myositis are listed, based upon anatomical and/or etiological factors. Some forms of myositis have been shown to be immune-mediated, some are suspected of being immune-mediated, others are infectious, and some remain idiopathic [315-317]. These myopathies share common histological features including presence of inflammatory cell infiltrates (the hallmark of myositis/polymyositis) and various degenerative changes in the muscle fibers. Note that inflammatory cells are also sometimes seen in muscles of animals with muscular dystrophy. Also note the caveat that "... absence of any inflammatory infiltrates in a biopsy does not exclude an inflammatory myopathy" [120].

### **Masticatory Myositis -**

This inflammatory myopathy (synonym is eosinophilic myositis) is one of the most common forms of myositis in dogs and is particularly common in adult, larger-breed dogs [318-322]. Results of one retrospective study indicated that most dogs were under 4 years of age with no gender or breed predilection [321]. This disease is characterized by recurrent inflammation of muscles, especially those of mastication (masseteric, temporalis, and pterygoid muscles), sometimes in association with peripheral blood eosinophilia. In most instances, the condition is restricted to muscles of mastication. This is an autoimmune disease in which B-lymphocyte-mediated antibodies are directed against type 2 M fibers in masticatory muscles. Type 2 M fibers are the dominant fiber type in masticatory muscles [323,324]. Biochemical studies have shown that masticatory muscles contain a unique myosin isoform, unique myosin light chains, and unique myosin heavy chains [325]. In one study of dogs with masticatory myositis, 86% of cases had autoantibodies fixed to type 2 M fibers of the temporalis muscle [326]. Incubation of normal muscle with sera from affected dogs resulted in labeling of 82% of type II M fibers. Immunocytochemical studies suggest that transforming growth factor-beta (TGF-beta) and latent transforming growth factor-beta binding protein (LTBP) may play a role in muscle tissue repair, inflammation and fibrogenesis in masticatory myositis [327].

Lesions consist of myonecrosis, hemorrhage, edema and multifocal or diffuse cellular infiltrates including macrophages, lymphocytes, plasma cells, occasional neutrophils, and rarely, eosinophils. Skeletal muscle fiber atrophy involving all fiber types may be pronounced, sometimes with foci of small round fibers comprising entire muscle bundles [321]. Fiber hypertrophy is usually not a feature. Perimysial and endomysial fibrosis is usually marked. Regeneration of muscle fibers, characterized by vesicular nuclear changes and fiber basophilia is frequently found.

Clinical signs are characterized by acute onset of painful, swollen, masticatory muscles. The jaw is held partially open (pseudotrismus) and passive manipulation is painful. Unilateral or bilateral exophthalmos may also be present [319], which in some cases may cause optic nerve compression or stretching resulting in blindness [321]. Dogs are often febrile, and tonsils and mandibular lymph nodes may be swollen. The acute phase may last 2 to 3 weeks, with signs reaching a peak by 10 to 14 days. Serum CK levels are elevated early in the disease and gamma globulin levels may be increased. Diagnosis is based on signalment, clinical, and muscle biopsy data, although histological demonstration of antibodies against type 2M fibers is also a sensitive index (the antibody titer may be reduced if corticosteroids have been administered previously). Prognosis is usually favorable. In most cases, the acute disease responds to corticosteroids, e.g., prednisone 1.0 to 2.0 mg/kg PO bid. The dose is reduced after remission of signs, and gradually withdrawn using alternate day therapy. Note that the lowest alternate-day dosage may be required for up to 6 months [317]. Repeated clinical episodes are not uncommon, which usually result in muscle atrophy. In one study, better clinical responses were noted in dogs receiving prednisone early in the course of the disease, for at least one month, and with the dosage tapered gradually from the initial immunosuppressive dosage [321]. Other immunosuppressive drugs such as azathioprine (at 0.6 mg/kg PO every one to three days) may also be used in conjunction with prednisone, with a steroid-sparing effect, or alone, to maintain remission. There is no apparent correlation between response to treatment and the extent/severity of the muscle lesions. Note that manual manipulation of the jaw carries an inherent risk of mandibular luxations/fractures [321]. In some severely affected dogs, there may be a permanent inability to adequately open the jaw, necessitating blending of the food for intake/ingestion [317].

Recently, a masticatory myositis has been reported in dogs with leishmaniasis (*Leishmania infantum*) [328] (see infectious myositis).

I have observed masticatory myositis in several cats and an autoimmune process is suspected. Note that many tissue samples received in our laboratory from dogs with suspected masticatory myositis have evidence of neurogenic atrophy with little or no sign of inflammation. These cases probably represent idiopathic trigeminal neuritis.

### **Atrophic Masticatory Myopathy/myositis -**

This is a chronic degenerative myopathy that is characterized by atrophy of muscles of mastication which can occur in dogs of any breed [329,330]. It has also been termed atrophic myositis and cranial myodegeneration. The pathogenesis of this condition is uncertain. It may be a stage of masticatory myositis or it might represent neurogenic atrophy secondary to idiopathic trigeminal neuritis associated with severe axonal degeneration. In some dogs with leishmaniasis, severe masticatory muscle atrophy may be present [331] (see infectious myositis). Atrophic masticatory myopathy may also be prominent in younger dogs with dermatomyositis. There is no peripheral or local eosinophilia present. The atrophy is accompanied by a state of trismus (lock-jaw) which may not be reduced, even under general anesthesia, and which may interfere with eating (although this is not a feature seen in dogs with leishmaniasis). Pathological studies reveal large numbers of atrophic fibers and increased perimysial connective tissue. Focal areas of lymphoplasmacytic infiltrates may

be seen occasionally in masticatory and other skeletal muscles.

Prognosis of this form may be guarded because of the severe trismus. However, in most dogs jaw function returns to normal. Some animals appear to respond to corticosteroids. Note that bilateral masticatory muscle atrophy may be seen in some cats with nemaline myopathy.

### **Polymyositis -**

Polymyositis is a relatively common myopathic disorder in dogs, but less common in cats. It has been suggested that polymyositis, masticatory myositis and other clinical variations, such as pharyngeal-esophageal and focal appendicular myositis, may represent different clinical and pathological expressions of a single primary muscle inflammatory disease [332]. The cause of polymyositis in dogs is not always known, although the responsiveness of the disease to immunosuppressive therapy suggests that the pathogenesis is immune-mediated. In people with polymyositis, the pathogenesis appear to involve cell-mediated immune mechanisms, with the inflammatory cells being mainly CD8+ T cells [333]. Polymyositis has been reported in dogs with specific autoimmune diseases, including systemic lupus erythematosus [334], primary lymphocytic thyroiditis, and immune-mediated polyarthritis (see below). Furthermore, it has been seen as an autoimmune paraneoplastic complication of thymoma, usually accompanied by myasthenia gravis [335,336]. Polymyositis and myasthenia gravis have also been reported in a dog following fetal liver transplant (see myasthenia gravis) and immunological mechanisms were considered to be involved [337]. Polymyositis is also a feature of dermatomyositis in Collie dogs and Shelties, another suspected immunological disease (see dermatomyositis).

Clinical signs are variable and are usually observed in larger breed, mature adults of either gender; however, there are reports in younger animals, including two 7 month old littermates [338]. Onset of signs may be acute or chronic. Signs may include acute vomiting and excessive salivation, weakness of gait with rapid fatigue, megaesophagus, dysphagia, shifting lameness and/or stiffness of gait, muscle swelling and/or pain, pyrexia, muscle atrophy, voice change and depression. Some dogs show signs of cervical ventroflexion [317]. Neurological examination is usually normal. Early in the disease, serum levels of CK, aspartate aminotransferase, alanine aminotransferase may be elevated but may not reflect the severity of clinical signs or the underlying muscle pathology (see below). Total serum protein may be elevated associated with increased  $\beta$ - and  $\gamma$ -globulin fractions. Some animals have positive antinuclear antibodies and circulating antimuscle antibodies. Electrodiagnostic changes include polyphasic motor unit potentials, positive sharp waves, and fibrillation potentials. Motor and sensory nerve conduction velocities are normal. Histopathological findings in skeletal muscle (appendicular and masticatory) are focal/multifocal or diffuse myonecrosis, phagocytosis and lymphoplasmacytic cellular infiltrates, endomysial/perimysial fibrosis, considerable fiber size variation, and areas of fiber regeneration. Rarely, eosinophilic cells may predominate [339]. Deposition of immunoglobulin G (but not C3 component) on sarcolemmal membranes has been demonstrated [340]. In dogs with polymyositis associated with leishmaniasis, IgG immune complexes are detected in muscle samples [328].

Diagnosis is based on clinical signs, increased serum levels of muscle enzymes, electromyographic abnormalities, and histopathological evidence of muscle necrosis and inflammatory cell infiltrates. Not all of these criteria may be found in any one animal. Diagnosis is definite if all criteria are present, probable if three are present, and possible if two are found [229]. Muscle enzyme activity is an unreliable index of polymyositis.

Prognosis is usually favorable for animals with polymyositis, provided inhalation pneumonia is not a complication, and severe damage has not occurred in esophageal and laryngeal muscles. The disease is usually responsive to corticosteroids, e.g., prednisolone at 1 to 3 mg/kg PO sid or bid. The dose is reduced after remission and gradually withdrawn using alternate day therapy. In some instances, long-term therapy for 12 months or longer may be required. Azathioprine may also be used in combination with corticosteroids and has a steroid-sparing effect [341]. Repeated clinical episodes are not uncommon. A fentanyl patch (25 - 50  $\mu$ g/h) for pain relief during the first 2 to 3 days has been recommended [317]. Prognosis is guarded in animals with thymoma because of the potential for malignancy and occurrence of other non-thymic tumors.

A connective tissue disorder characterized by non-erosive polyarthritis and polymyositis has been reported in 6 young adult dogs [518]. Clinical signs included stiffness, joint swelling, joint pain, muscle atrophy, muscle pain and contracture and the presence of chronic active inflammation (lymphocytes, neutrophils, macrophages, and plasma cells) in biopsies of muscle and synovium. There was no muscle fiber immunofluorescence. Systemic lupus erythematosus was excluded by the absence of circulating antinuclear antibody. 5 of the dogs were of Spaniel breeds. Prognosis was poor with only 2 dogs recovering after treatment with cyclophosphamide (2 mg/kg on 4 days each week) and prednisolone (1 mg/kg/day) for 2 months. In another report, however, 2 dogs with this condition (signs included lethargy, exophthalmos, muscle pain, and atrophy of masticatory/appendicular muscles) responded favorably to immunosuppressive corticosteroid therapy [519].

Polymyositis occurs sporadically in cats [342], sometimes in association with thymoma [343]. The inflammatory infiltrates are predominantly mononuclear, with small lymphocytes and macrophages. Neutrophils are seen infrequently. Eosinophils are rare. A polymyositis has also been observed in cats usually over 1 year of age, without breed or sex predisposition [117], and while the cause was not defined, many affected cats were hypokalemic (see hypokalemic myopathy). Pathological findings included myonecrosis, lymphocytic cellular infiltrates, internal nuclei and fiber

regeneration. Clinical signs were characterized by a persistent ventroflexion of the neck, appendicular weakness especially in the thoracic limbs, painful muscles and exercise intolerance. Serum levels of CK and aldolase were elevated. Electromyography revealed fibrillation potentials, positive sharp waves and bizarre high-frequency waves. Prognosis was guarded. Some cats recovered spontaneously while others appeared to respond to corticosteroids. Recurrences were observed.

We have seen suspected immune-mediated, mononuclear polymyositis in muscles of several cats, including samples from one cat with myasthenia gravis and thymoma. In muscle samples from another cat with myositis, numerous muscle fibers stained positively with staphylococcal protein A-horseradish peroxidase.

### **Extraocular Myositis -**

This condition has been reported in dogs aged between 6 months and 3 years [344-346]. It appears to be more often reported in Golden Retrievers, but other breeds include Doberman Pinscher, German Shepherd and mixed-breed dogs. Male and female dogs may be affected. The dominant clinical sign is acute bilateral exophthalmos, although unilateral involvement has been noted. Extraocular muscle myositis and restrictive strabismus (unilateral or bilateral) has been reported in 11 dogs of different breeds [346,347]. Clinically, abnormalities are restricted to the extraocular muscles with sparing of the masticatory muscles and limb muscles. An immune mechanism directed against specific muscle fiber antigens in the extraocular muscles is suspected. Direct and indirect pupillary reflexes and fundic examination are normal. Visual impairment may be present and intraocular pressure may be elevated [344]. Swelling of extraocular (extrinsic) muscles may be detected using ultrasonography or computer tomography [346]. EMG studies reveal presence of fibrillation potentials and positive sharp waves. Fine needle aspirate biopsies can be diagnostic. In one study, macroscopic findings were confined to the extraocular muscles, the central zones of which appeared swollen and pallid, while microscopically, there was severe lymphocytic inflammation with variable, mild plasmacytic, neutrophilic and eosinophilic infiltrates, multifocal necrosis, phagocytosis, basophilia, internalized nuclei, slight fibrosis, and occasional foci of hemorrhage [344]. No abnormalities were seen in blood vessels or nerves.

Oral corticosteroid therapy for two weeks usually results in complete resolution of signs. Relapses may occur but usually respond well to a second treatment. No dogs exhibit clinical signs of hypothyroidism. Surgical correction may restore eye position and vision in dogs with restrictive strabismus [347].

### **Dermatomyositis -**

Dermatomyositis or familial canine dermatomyositis is a well documented disease of Collie dogs, of all coat colors and both coat lengths. Dermatomyositis has also been reported in the Shetland Sheepdog (Sheltie), Beauceron Shepherd, Pembroke Welsh Corgi, Australian Cattle dog, Lakeland Terrier, Chow Chow, German Shepherd, and Kuvasz [348-355]. The condition is considered to be inherited as a dominant trait with variable expressivity in Collies and in Shetland Sheepdogs [355,356]. Cutaneous lesions involving the face, lips, ears, and skin over bony prominences of the limbs, feet, sternum, and tip of the tail are noted usually between 2 and 6 months of age. Male and females can be affected. Other clinical signs range from generalized weakness and exercise intolerance, to difficulty in lapping water, chewing and swallowing. Megaesophagus may lead to inhalation pneumonia. Generalized or localized muscle atrophy may be noted, especially of muscles of mastication and distal limbs. Cutaneous pain is often seen in Beaucerons.

Dermatomyositis is an inflammatory disease of muscle and skin, and sometimes blood vessels. The cutaneous lesions consist of pustules, ulcers, and vesicles which may progress rapidly to crusted or alopecic areas. Myositis develops several months later and principally involves muscles of mastication and muscles of the extremities below the elbow and stifle. The muscle lesions appear to be correlated with the severity of the skin lesions. Muscle lesions consist of multifocal muscle fiber necrosis, internalization of muscle nuclei, atrophy, fibrosis, and regeneration, and mild to severe interstitial and perivascular inflammatory cell infiltrates (lymphocytes, neutrophils, plasma cells, and macrophages). Small intrafascicular nerves may be surrounded by inflammatory cells. Vasculitis is seen in skin, muscle, and occasionally in other tissues. Necrotizing vasculitis of small venules and arterioles is characterized by fibrinoid thickening of the vessel wall, pyknosis and karyorrhexis of endothelial cell nuclei, and neutrophilic inflammation [357]. In many cases, the lesions spontaneously regress by 6 to 8 months of age, although severely affected dogs may have dermatitis throughout their lives. Differential diagnosis of the skin lesions includes demodicosis, dermatophytosis, staphylococcal folliculitis, epidermolysis bullosa simplex, and discoid lupus erythematosus [355].

This condition is believed to be immune-mediated, although some clinicians favor an infectious etiology [358]. Others have suggested it is a subset of lupus erythematosus [359]. A type III hypersensitivity reaction may be involved in the pathogenesis [357]. Autoantibodies to muscle or skin have not been demonstrated, and antinuclear antibody titers and lupus erythematosus cell testing are negative. Coombs' test may be positive. There is a dramatic increase in serum concentrations of IgG and circulating immune complexes, which may be detected before clinical signs and which show a positive correlation with disease severity, and which decline as animals enter remission [357]. There is no deficiency of complement (C3, C2, C4, or CH50) [360]. In people with dermatomyositis, the capillary lining is thought to be the target of the circulating immune complexes, and perifascicular muscle atrophy may be a consequence of ischemic changes secondary to endomysial vasculopathy [333]. Non-regenerative anemia due to chronic inflammation may occur in severely affected dogs. CK levels are usually normal but may be increased. Cerebrospinal fluid analysis and nerve

conduction studies are normal. The presence of fibrillation potentials, positive sharp waves, and bizarre high frequency discharges has been demonstrated electromyographically.

The cyclic and self-limiting nature of this disease complicates treatment evaluation. Rarely, affected adult dogs may die from acute renal failure as a result of severe secondary amyloidosis [361]. Hypoallergenic shampoos are beneficial. Prognosis tends to be guarded, especially in severely affected dogs. Prednisolone, at 1 to 2 mg/kg PO bid, may be effective in some animals [355]. If improvement is seen, the dosage should be tapered to alternate day therapy. Vitamin E (200 - 800 U daily PO) or marine lipid supplements may be useful in refractory cases. Pentoxifylline may be included as a corticosteroid-sparing drug. (at 200 - 400 mg q24 - 48h). Dogs with disease remission by 1 year of age tend to have a good prognosis [357]. Note that muscle disease may progress as skin lesions regress leading to severe muscle atrophy in some older dogs, and with potential problems in eating and drinking due to masticatory muscle atrophy.

### **Myositis Ossificans -**

Myositis ossificans or ossifying myopathy, perhaps a misnomer (see below), is an uncommon myopathic disorder of animals that is characterized by heterotopic ossification of skeletal muscle. Local and generalized forms of this disease have been reported in dogs and cats [46,362-364]. The etiopathogenesis is uncertain. Trauma may be associated with localized, ossifying myopathy [46,365], but it is not a prerequisite. Focal masses have been reported adjacent to the zygomatic arch and near the coxofemoral joint in dogs. The generalized form in people is suggested to be congenital or hereditary in nature.

Histopathological lesions of focal myositis ossificans in animals vary from mild interstitial fibrosis, to complete replacement of muscle by fibrous tissue and heterotopic bone. In one report, the mass was well circumscribed with fibrous tissue around the periphery, then cartilage, and cancellous bone with bone marrow/fibrous tissue centrally [366] (this may have been a case of heterotopic osteochondrofibromatosis). Focal masses need to be differentiated from extraskeletal osteosarcomas [367]. The generalized form is characterized by fibrosis, muscle fiber degeneration, mononuclear myositis, muscle atrophy, dystrophic calcification, and ossification [363]. Clinical signs of the focal form are usually associated with lameness. In one dog with a focal mass near the zygomatic arch, the jaw could not be opened more than 3 cm. In the generalized form, signs are variable and may include progressive weakness, swollen muscles, muscle pain, stiffness, and palpable firm enlargements in affected muscles. We have seen generalized myositis and calcification in muscle samples from a 4 year old female Domestic Shorthaired cat with a history of relapsing weakness. Muscles were firm, serum CK levels were very high, and myoglobinuria was noted. Electromyographic testing revealed diffuse abnormal potentials that were more severe in proximal muscles. Muscle lesions were characterized by diffuse mineralization (calcium deposits that stained positively with Alizarin Red), disseminated necrosis and phagocytosis, mononuclear cell infiltration, and fibrosis. At necropsy, multifocal white areas were observed in most skeletal muscles. The cause of this apparent generalized myositis ossificans was not determined.

Radiographic studies of myositis ossificans may reveal focal or multiple soft tissue radiopacities of irregular linear calcification, along with variable periosteal reactions [363,368]. Prognosis is guarded in animals with generalized myositis ossificans; however, surgical excision of focal masses has been performed successfully [366,368]. In some cases, focal lesions may regress. In people, the more generalized form of myositis ossificans may be seen as a complication of dermatomyositis in childhood [7].

As mentioned above, the term "myositis ossificans" may be too simple, or even incorrect, in some reported cases in animals. For example, another condition seen occasionally in cats, termed fibrodysplasia ossificans, differs from myositis ossificans in that it does not primarily involve muscle, is multicentric, often symmetrical, and unrelated to trauma [369-371], and Valentine and colleagues [372] have included the above-mentioned cases of generalized myositis ossificans, progressive ossifying myositis, and fibrodysplasia ossificans under the category of fibrodysplasia ossificans progressiva (FOP). Absence of muscle fiber lesions and lack of abnormal EMG findings in some animals are more commensurate with a primary connective tissue disorder associated with fibrovascular proliferation, chondroid and osseous metaplasia in epimysium, tendons/ligaments, or fasciae, than a primary defect of skeletal muscle (any muscle changes present may be secondary to the connective tissue disease) [372]. In people, FOP is an extremely rare hereditary disorder (autosomal dominant) of connective tissue characterized by progressive heterotopic ossification of the tendons, ligaments, fasciae, and striated muscles [373]. Other forms of heterotopic calcification in dogs occur with calcinosis circumscripta/tumoral calcinosis. Recently, bilateral cervical heterotopic ossification associated with a thoracic limb lameness, was reported in an adult German shepherd dog [374]. Hard, non-painful masses were palpable under the cranial border of the scapula in both forelimbs. Radiographs revealed two mineralized densities ventrolateral to the lateral processes of the 6th cervical vertebra. These lesions appeared to be adjacent to the tendons of insertion of the longissimus cervicis muscles that attach to the lateral processes of the 6th cervical vertebra. The lameness resolved following surgical removal of one of the masses. The lesion was classified morphologically as fibrodysplasia ossificans, and it was postulated that the heterotopic ossification resulted from the metaplastic change of calcinosis circumscripta lesions.

### **Laryngeal Myositis -**

I have seen myositis in laryngeal muscles of several dogs (a 7 year old male Boykin Spaniel; a 10 year old male Malamute; and a 3 year old Bouvier des Flandres) presented with signs of chronic laryngeal paralysis and dysphagia.



Laryngeal muscle changes included multifocal myonecrosis, phagocytosis, mononuclear cell infiltrates, and variable fibrosis. Intramuscular nerve bundles appeared normal although there was mild evidence of neurogenic atrophy in laryngeal muscles of all three dogs. Electromyographic studies on laryngeal and/or esophageal muscles revealed fibrillation potentials, positive sharp waves, and high frequency, bizarre discharges. With the exception of mild, focal inflammation seen in temporalis muscle from one dog, pathological and electrodiagnostic changes were restricted to laryngeal / pharyngeal muscles. Laboratory tests were normal in all dogs. The etiopathogenesis, treatment and prognosis of this condition remain to be determined. Prognosis is guarded to favorable: one dog was euthanized because of respiratory distress, a castellated laryngoplasty was performed on one dog, and the third dog that was marginally hypothyroid, responded to thyroid hormone replacement and corticosteroids.

### **Infectious Myositis -**

Infectious myositis is most commonly seen in dogs with several protozoon diseases, including hepatozoonosis and toxoplasmosis and neosporosis. Myositis also occurs with trypanosomiasis. More recently, myositis has been reported with leishmaniasis, an endemic protozoan disease in Mediterranean countries and Portugal that is caused by *Leishmania infantum* [328,331]. The disease usually occurs in older dogs (with a range from 1.5 to 10 years) and affects dogs of either gender and of various breeds. Clinical signs include skin lesions (e.g., exfoliative dermatitis and skin ulcerations) and atrophy of the masticatory muscles. In some dogs, there is also appendicular muscle atrophy. The masticatory atrophy tends to be insidious, slowly progressive, usually unassociated with trismus. Exercise intolerance, megaesophagus, or gait disturbances are not seen. In some dogs, the myositis is subclinical. Serum CK levels are often elevated, especially in those dogs with severe muscle atrophy. EMG studies reveal positive sharp waves, fibrillation potentials, and bizarre, high frequency discharges. Nerve conduction studies are normal. Histological changes in muscle include myofiber necrosis, degeneration, regeneration, with varying degrees of atrophy, along with fibrosis, interstitial and/or perivascular mononuclear cell infiltration (macrophages, lymphocytes, occasional plasma cells), and neutrophilic vasculitis, sometimes with mild to severe thrombosis. Leishmanial amastigotes are frequently seen within macrophages and skeletal muscle cells. IgG complexes are found within myofibers and also on the sarcolemma, and circulating antimyosin antibodies are found in serum. While the exact pathogenesis of the muscle lesions remains uncertain, the immunological findings suggest at least partial immune-mediated pathology. Other muscle changes might be related to ischemia secondary to vasculitis/thrombosis. The vasculitis is considered to be the result of a type III hypersensitivity reaction.

Prognosis is guarded. Note the zoonotic potential for leishmaniasis. Treatment is complicated due to resistance to therapy of *Leishmania* organisms; however, allopurinol (at 7 - 15 mg/kg PO bid for 26 weeks) has been recommended, although complete recovery is rarely achieved [375].

Bacterial myositis is reported sporadically in dogs and cats. Normal muscle in people is resistant to bacterial infection and suppurative myositis is rarely seen [376]. Polymyositis associated with *Leptospira australis* infection was documented in a 10 year old male greyhound [377]. Signs included fever, severe back pain, arched back and semiflexed limbs, and reluctance to stand. Neurological examination was normal. Electromyography revealed generalized abnormal spontaneous potentials. Serum CK levels were markedly elevated. Other findings included red colored urine (attributed to the presence of myoglobin), neutrophilia, and positive titer for *L. australis*. Clinical signs abated somewhat with non-steroidal inflammatory anti - inflammatory medication and amoxicillin. Polymyositis has also been seen with *Leptospira icterohaemorrhagiae* [378]. There are several reports of clostridial myositis (e.g., associated with *C. chauvoei* and *C. septicum* infection) in dogs and cats, often in association with muscle wounds/injuries, or surgical procedures [379-385]. Pain, swelling, and lameness may be seen with limb involvement. Grossly, crepitant swelling, subcutaneous edema and black, emphysematous muscles are often found. Histologically, hemorrhages, congested vessels, myofiber necrosis, and variable neutrophilic infiltration is seen in affected muscles [381].

Treatment usually requires radical surgical aeration, along with appropriate antibiotics, e.g., clavulanate potentiated amoxicillin at 22 mg/kg PO bid for 5 - 7 days, in combination with metronidazole, at 10 mg/kg PO bid or tid (dog) (or 62.5 mg, PO bid for cats) for 5 - 7 days, and allowing healing by secondary intention [379]. Less frequently, myositis may occur with migrating parasites and rickettsial disease (also see rickettsial meningoencephalitis) [386,387].

Trichinosis myositis associated with *Trichinella spiralis* has been observed in a 6 year old female Fox Terrier used for badger hunting with signs of acute onset weakness [388].

Viral myositis appears to be rare in dogs and cats; however, an inflammatory myopathy was experimentally-induced in adult cats using feline immunodeficiency virus [389]. The predominant histologic abnormalities consisted of perivascular and pericapillary lymphocytic infiltration (CD8+ lymphocytes), myofiber necrosis, phagocytosis, and regeneration.

### **Paraneoplastic Myositis -**

Low-grade myositis is seen sporadically in dogs with malignant tumors, such as bronchogenic carcinoma, myeloid leukemia, and tonsillar carcinoma [378,390] and it is thought to represent a paraneoplastic complication (see paraneoplastic syndromes).

### **Drug-induced Myositis -**

A polymyositis reportedly occurred in several Doberman Pinschers as part of a multisystem allergic drug reaction (type III hypersensitivity) following treatment with sulfadiazine [391]; although supporting evidence from electrodiagnostic studies or muscle biopsies were not provided.

### **Myotonic Myopathy**

Myotonia refers to a state in which active contraction of a muscle persists after cessation of voluntary effort or mechanical/electrical stimulation. This condition is characterized by muscle spasm (stiffness) and by temporary inability to initiate movement. Myotonia may be clinically observed, noted during EMG studies, or both. Reduced muscle membrane chloride conductance leading to membrane hyperexcitability, after-depolarization and repetitive firing, is the underlying mechanism responsible for congenital myotonia in children (including both the autosomal dominant Thomsen's disease and autosomal recessive Becker's disease) [9,392]. A similar chloride channelopathy occurs in goats with Thomsen's disease [393,394]. Paramyotonia congenita (autosomal recessive) is one of several recently classified sodium channelopathies in people [395,396]. In contrast, dystrophic myotonia (myotonic dystrophy or Steinert's disease) is an adult-onset, non-channelopathy, autosomal dominant, multisystem degenerative disease occurring in people characterized by myotonia, progressive muscular weakness, gonadal atrophy, cataracts, and cardiac dysrhythmias [4]. Myotonia is also sometimes seen in human patients with hyperkalemic periodic paralysis (see hyperkalemic myopathy) associated with a sodium channelopathy [9]. Congenital and acquired forms of myotonia have been reported in dogs, and congenital myotonia has been seen in cats. Congenital myotonic myopathy (*myotonia congenita*) has been reported in male and female Chow Chows, Staffordshire Terriers, Great Danes, and Miniature Schnauzers [397-407]. These conditions are considered to be inherited (probable autosomal recessive in Chows and Staffordshire Terriers), although results of breeding trials await confirmation. Spontaneous mutations are likely in the sporadic cases reported. However, in the Miniature Schnauzer puppies, the myotonia congenita is autosomal recessive and caused by a mutation in the skeletal muscle voltage-dependent chloride channel, CIC-1 [407,408]. A multisystem membrane defect associated with low serum cholesterol was suggested in Chow Chows [400]. Congenital myotonia has also been reported in male and female kittens [409-411]. The condition in cats is thought to be inherited and the disease is currently being investigated. Clinical signs in puppies may be seen as early as 2 to 3 months of age. Signs include stiffness in the first movements after a period of rest, splaying of thoracic limbs, and a bunny hopping pelvic limb gait. Dogs will remain in rigid hyperextension in lateral recumbency for up to 30 seconds if they are suddenly rotated onto their sides. Affected dogs may not be able to climb stairs or mount raised platforms. Some dogs may manifest dysphagia and respiratory difficulty from stenosis of the glottis. Laryngeal paralysis was noted in the Miniature Schnauzers. Stiffness and weakness largely disappear with exercise. Most skeletal muscles can be hypertrophied, especially proximal limb muscles, neck muscles and tongue. Signs are worse in cold weather. In older animals, an increasing period of exercise is necessary for muscle relaxation to occur. Percussion of muscles results in formation of dimples. This reaction is elicited in conscious and anesthetized dogs, and in those administered neuromuscular blocking agents. In kittens, the gait is also stiff and stilted (limbs tend to be abducted), especially in the hind limbs, and signs are also worse in cold weather and improve with exercise [410,411]. There may be marked non-painful enlargement of proximal appendicular muscles. When startled, all four limbs become extended and kittens fall into lateral recumbency. Other signs seen on being startled include third eyelid prolapse, spasm of the orbicularis oculi muscle, lip retraction, and ear flattening. Masticatory muscle spasms may result in trismus, which may lead to dysphagia. Dysphonia and inspiratory stridor (sometimes with cyanosis) is seen occasionally. Some kittens have a coarse meow. Electromyographic studies in dogs and cats are characterized by trains of repetitive discharges which wax and wane in frequency, producing an audible "dive-bomber" or motorcycle sound. These myotonic discharges are independent of neural control and persist even under general anesthesia [412]. A regional curare test for evaluating muscle discharges without subjecting animals to general anesthesia has been reported [413]. Motor and sensory nerve conduction velocities are normal. Myopathic changes are mild and typically non-specific with occasional fiber hypertrophy, centralized nuclei, and focal necrosis. Histochemical stains and dystrophin immunocytochemistry are normal in dogs and cats. A deficiency in type I fibers has been reported in Staffordshire Terriers [399]. Mild dilatation of transverse tubules have been seen in affected kitten muscle by electron microscopy [410]. No abnormalities are seen in peripheral nerves. Serum creatine kinase levels are normal or slightly elevated. Hypocholesterolemia has been reported in one affected Chow Chow [400], while serum cholesterol levels were normal in kittens [411]. Diagnosis is based on signalment, clinical and electrodiagnostic data. Prognosis is guarded, although myotonia congenita does not appear to be progressive. Membrane stabilizing agents including procainamide (at 40 mg/kg PO qid) and mexiletine (at 8.3 mg/kg PO tid), as well as quinidine and phenytoin, may result in significant improvement in clinical signs [406]. These drugs act by blocking voltage-dependent sodium channels thereby decreasing membrane excitability (drugs acting on the chloride channel are not presently available). Note that these membrane stabilizing drugs have a high risk of side-effects in cats [411]. To date, no treatment has been necessary in the affected kittens (close supervision is advised, however). Anesthesia may also be a risk in affected animals due to difficulty in endotracheal intubation associated with an inability to open the mouth to a wide angle, enlargement of the tongue and pharyngeal muscles, or narrowing of the glottis due to muscle spasm or paralysis [400,406,410,411]. Potassium bromide may be contraindicated in dogs with myotonia congenita [414].

Adult-onset myotonic myopathy has been reported as an idiopathic condition in several dogs, including a 3 year old Rhodesian Ridgeback dog [415], a 3 year old Boxer [416], and 11 and 13 year old female Poodles [417]. Clinical signs and electrodiagnostic findings are similar to those seen in dogs with myotonia congenita. Serum CK levels are elevated. Histopathological changes tend to be much more obvious, and these may include fiber size variation, fiber splitting, occasional myonecrosis, many fibers with internalized nuclei, and type I fiber deficiency. Note that similar changes have been noted in adult dogs with myotonia congenita. Immunohistochemical staining is positive for dystrophin [416]. No changes are seen in peripheral nerves. Clinical (e.g., weakness, stiff gait with short stride, tonic extension of all limbs and falling, palpably firm skeletal muscles and myotonic dimpling) and electromyographic evidence of myotonia has been observed in dogs exposed to herbicides containing 2,4-dichlorophenoxyacetic acid (2,4-D) or 2-methoxy-3,6-dichlorobenzoic acid (dicamba or MCPA), and serum CK levels may be markedly elevated [418-421].

Secondary myotonia occurs in several other myopathic disorders in dogs, including hyperadrenocortical (Cushing's) myopathy, hypothyroid myopathy, Labrador Retriever hereditary myopathy, and the dystrophinopathies in dogs and cats (see muscular dystrophy). In these conditions, electrophysiological evidence of myotonic-like discharges may be seen and heard [72,75,137,174,181,263,295,309,398,412,413,422]. However, since these discharges typically do not wax and wane, they have been termed "pseudomyotonic" or "bizarre high frequency discharges" [412]. An overlap of true myotonic and pseudomyotonic discharges may occur in some instances. For example, Duncan and colleagues reported that of 5 dogs with Cushing's disease, waxing and waning discharges were recorded in four dogs, and pseudomyotonic potential in one dog [71]. Curiously, myotonic discharges that waxed and waned were noted in one study of dogs with fibrotic myopathy [36]. Note that clinical myotonia may occur secondary to Cushing's disease in some dogs, with signs including stiffness, muscle hypertrophy, muscle dimpling, rigid epaxial muscles, arching of the back, ears drawn back, and tongue protrusion [71,72,75,417].

### **Nemaline Myopathy**

In people, nemaline myopathy is a disorder characterized morphologically by the presence of rods (nemaline bodies) in muscle cells. Various forms of the disease have been reported, including congenital, childhood-onset and adult-onset, and both autosomal dominant and autosomal recessive cases have been documented [423]. Three genetic mutations have been identified as the cause of nemaline myopathy: the gene for slow alpha-tropomyosin 3, the nebulin gene, and the actin gene. Nemaline myopathy appears to be most commonly associated with the autosomal recessive form caused by mutations in the nebulin gene [424]. The pathogenesis of nemaline myopathy is still unclear although recent molecular genetic studies suggest that rod formation is secondary to contractile dysfunction [425]. The main component of the nemaline bodies is  $\alpha$ -actinin [426]. Nemaline myopathy has been infrequently reported in animals. In 1986, Cooper and associates reported on nemaline myopathy in 5 cats, of either gender, derived from 4 litters from the same mother, thus suggesting possible autosomal recessive mode of inheritance [427]. Clinical signs were observed in cats (a specific breed was not reported) between 6 months and 1.5 years of age. Cats appeared extremely apprehensive. Signs included mild weakness, reluctance to move, and a crouched, jerky hypermetric gait when prompted to move. Following a short period of movement, some cats appeared fatigued and panted. In some animals there was skin twitching and muscle atrophy (especially in scapular and gluteal muscles, and occasionally, in masticatory muscles). Patellar reflexes were consistently depressed or absent. Other spinal reflexes, along with sensation, were normal. Electrodiagnostic studies and cerebrospinal fluid analyses were normal, although mild increase in serum CK and lactate dehydrogenase levels were seen in some cats. Prognosis was poor. Clinical signs persisted for up to a year after signs first began, but did not appear to progress. However, muscle atrophy did progress, and cats became inappetent, lost condition, and were eventually euthanized. Pathological findings were characterized by presence of large numbers of nemaline rods in skeletal muscle fibers (while all muscles examined were abnormal, the changes were most apparent in the proximal forelimb muscles), marked fiber size variation, atrophy of type 1 and type 2A fibers, internalized nuclei, and fiber splitting. In some muscles, core-like lesions were seen characterized by disorganization of the internal structure producing a swirling pattern and particularly evident on NADH-TR-stained myofibers. Rods stained red with trichrome stain and were aligned along the long axis of muscle fibers (in some instances measuring up to 5.7  $\mu$ m in length). Rod numbers varied from a few to many (that filled some fibers) and were in subsarcolemmal or central locations. Rods were most common in atrophic type 1 and type 2A fibers. Predominance of type 1 fibers, typically a feature of the human disease [428,429], was not observed. Ultrastructurally, there was myofibrillar disarray. Rods were electron-dense and showed bi-directional periodicity (approximately 17 nm along the axis and 8 nm transversely) in longitudinal sections, and a lattice-like arrangement in cross-sections. Rods appeared to arise from Z-bands and the smallest rods consisted of localized expansions of the Z-band. No lesions were seen in extraneural tissues, brain, spinal cord, or peripheral nerves. Nemaline rods have been experimentally-induced in cats by tenotomy [425]. Congenital and adult-onset nemaline myopathies have also been reported in several dogs, including a 12 week old female Silky Terrier [230], a 10 month old Border Collie, and an 11 year old Schipperke with a 5 year history of gait abnormalities [430]. Clinical signs are somewhat variable but may include exercise intolerance and limb tremors, stiff-stilted gait (in hind limbs or in all four limbs), and spasmodic limb jerking. In some instances, a plantigrade stance has been noted in the thoracic limbs, there may be generalized muscle hypertrophy, and sometimes absence of patellar reflexes along with decreased withdrawal reflexes. In one affected dog,

there was a history of dysphagia/choking, the tongue was protruded, and the dog assumed a "begging" position after mild exercise [230]. EMG changes in these young dogs were usually mild (occasional fibrillation potentials and positive sharp waves), and nerve conduction velocities were normal. Muscle changes in affected dogs include presence of numerous rods, especially in atrophic type 1 fibers. Type 1 fiber predominance was reported in one dog with most fibers having a lobulated appearance [430]. Ultrastructural findings are similar to those seen in cats. As in people, rods are not exclusive to nemaline myopathy and have been seen in normal canine muscle in fibers adjacent to thick fibrous septa/tendinous insertions [431], occasionally in adult dogs associated with hypothyroidism [137,432] and Cushing's syndrome [430] (although concurrent hypothyroidism may have complicated the Cushing's syndrome in this report), and in older Golden Retrievers with muscular dystrophy [264]. The significance of the rods in these various other canine myopathies remains to be determined.

### **Polyglucosan Myopathy**

A myopathy may be found in some dogs with progressive myoclonic epilepsy (see Lafora's disease that is characterized by presence of periodic acid-Schiff positive polyglucosan inclusions in a variety of tissues including skeletal muscle, peripheral nerve, and CNS).

### **Toxic Myopathy**

There have been sporadic reports of a severe myopathy in dogs associated with ingestion of dog food contaminated with monensin, a coccidiostat and feed additive used for chickens and cattle [24,433]. In one report in which 17 dogs were exposed, 14 died [24]. Clinical signs included polydipsia, polyuria, dark urine, vomiting, lethargy/weakness, anorexia, dehydration, and diarrhea. In cases we have seen, morphological changes are characterized by acute necrosis, muscle fiber degeneration, fiber atrophy, regeneration, and fibrosis. Organophosphates have been incriminated in skeletal muscle necrosis in dogs (see organophosphate/carbamate toxicity).

### **Vitamin E Myopathy**

Vitamin E (alpha tocopherol) myopathies (variously termed white muscle disease, nutritional myopathy, and nutritional myodegeneration) have been reported in sheep, cattle, pigs, horses, and poultry (often in conjunction with selenium deficiency), but only rarely in dogs or cats [434-438]. This myopathy is associated with low dietary levels of vitamin E, although similar clinical signs and pathology occur in dogs with experimental vitamin E and selenium deficiency [439]. Selenium is an integral part of glutathione peroxidase and its function is closely involved with that of vitamin E. Clinical signs include of vitamin E (vitamin E/selenium) myopathy include weakness, dysphagia, sialosis, dysphonia, stiff stilted gait, difficulty in rising from a recumbent position, and inability to raise heads. Sudden death is reported in newborn puppies. Signs may be exacerbated with exercise. Serum muscle enzymes are often elevated, especially CK levels [440]. Skeletal muscle lesions tend to be bilaterally symmetrical and may affect individual or several muscle groups. Grossly, the affected muscle is paler than normal and distinct chalky longitudinal striations may be visible. Pathological findings are characterized by necrosis, phagocytosis, proliferation of sarcolemmal nuclei, loss of striations, and fiber regeneration. Mineralization may be seen in necrotic muscle fibers. Myocardial necrosis is also a feature of vitamin E/selenium deficiency [434,435,439,441]. Diagnosis is based on historical, clinical, and histopathological data. Animals usually recover rapidly after selenium and/or vitamin E replacement therapy. A confirmed case of a myopathy due to a deficiency of vitamin E has been reported in a 2 year old female cat that was fed a diet consisting almost entirely of boiled Norwegian coley [442]. Muscles in the pelvic limbs were swollen, hot and very painful on palpation. Histological muscle changes were similar to those reported in dogs. Complete clinical recovery occurred within 14 days following correct dietary management and multivitamin supplementation (especially vitamin E additives). Recent studies [19] suggest that vitamin E does not appear to play a role in sled dogs developing exertional rhabdomyolysis. For more information on vitamin E and the CNS, see vitamin E deficiency.

### **Myasthenia Gravis**

Myasthenia gravis (MG) is a disorder of the neuromuscular junction and both acquired and congenital forms of the disease are recognized in animals and in humans.

Acquired MG is now recognized as a common condition in dogs [443-448] (although it is less commonly reported in cats) characterized by failure of neuromuscular transmission due to reduction in number of functional nicotinic acetylcholine receptors (AChR) on the post-synaptic membrane of the neuromuscular junction [449-451]. This deficiency of receptors reduces the sensitivity of the postsynaptic membrane to the transmitter, acetylcholine. Acquired canine MG is an immune-mediated disease caused by production of antibodies (predominantly IgG) directed against acetylcholine receptors (AChR-ab) of the neuromuscular junction [452]. Reactive antibodies are usually demonstrable in the sera of dogs (approximately 98%) with acquired MG [443] and in most affected cats [453-457]. Antibodies reactive with muscle striations and other autoantibodies (see below) may coexist with a high titer of AChR-ab. Based on experimental and human clinical studies, MG involves both B and T cells (T cells and complement are involved in persistent B cell stimulation and in cell-mediated postsynaptic destruction of the neuromuscular junction, and there is antibody-induced blockade of the function of the remaining AChR molecules) [458,459]. In people, the thymus (either

hyperplastic or neoplastic) appears to play an important role in the pathogenesis of MG [459,460,531]; thymic dysfunction may occur in 75% of human patients with MG [461]. Acquired MG in dogs and cats also occurs in association with thymic dysfunction, including thymomas [451,456,462-473], other thymic abnormalities such as thymic cysts [457,474,534], or non-neoplastic thymic disease [474]. Some cysts (thymic or brachial cleft cysts) have apparent T-cell infiltration [534]. The reported incidence of thymoma is approximately 3% in dogs [448] but is much higher in cats, with an incidence ranging from 19 to 25% [444,475]. In these animals, the pathogenesis of the autoimmune response of acquired MG remains unclear but may be paraneoplastic and related to the recognized antigenic similarity between myoid cells of the thymus and receptor-bearing muscle cells at the neuromuscular junction. One theory is that disruption of the thymic lymphocytes or muscle cells may lead to an autoimmune attack against acetylcholine receptors and other skeletal muscle components [476,477]. Human patients with thymoma-associated MG may also produce autoantibodies to a variety of neuromuscular antigens, including the muscle protein titin, skeletal muscle calcium release channel (ryanodine receptor, RyR), and voltage-gated potassium channels [478,531]. Titin and RyR antibodies have been recently detected in dogs with thymoma-related MG, as well as in dogs with other forms of MG [451]. The presence of circulating RyR antibodies seems to be associated with a severe form of thymoma associated myasthenia gravis in human and canine patients [443,479]. Occasionally, MG may develop in dogs and cats after removal of the thymoma [468,480]. In dogs, acquired MG has also been reported in association with other tumors including cholangiocellular carcinoma [481], osteogenic sarcoma [482], anal sac adenocarcinoma [475], and non-epitheliotropic cutaneous lymphoma [483]. Acquired MG and polymyositis developed in one dog following fetal hematopoietic cell transplantation, along with presence of AChR-ab and immune complexes reactive with myoneural junctions [484]. Acquired MG has also been reported in dogs with hypothyroidism [485], and in hyperthyroid cats receiving tapazole (methimazole) therapy [486], a drug known to exacerbate MG in people [487]. Shelton states that she has identified MG in dogs with hypoadrenocorticism, thrombocytopenia, and hemolytic anemia [443].

Acquired MG has been observed in adult dogs of all sizes, but more commonly in medium-to-large breeds, and particularly in German Shepherds, Golden Retrievers, and Labrador Retrievers [448,452,463]. In one report, the relative risk of acquired MG in different breeds of dogs was highest in Akitas [448]. Newfoundlands may also be predisposed to acquired MG [488]. A bimodal age of onset (<5 years and >7 years) has also been reported in affected dogs [452], and spayed female dogs may have heightened risk [448] (a bimodal incidence peak is also seen in people: second and third decades in women, and fifth and sixth decades in men [459]). In one review of cats with acquired MG, Abyssinians and a close relative, Somalis, usually > 3 years of age, seemed to be overrepresented (gender was not a risk factor) [444]. A spectrum of clinical signs occurs in animals with MG, along with some variations between cats and dogs. Signs in dogs are often characterized by generalized muscle weakness/fatigability that is exacerbated by exercise. Additional signs may be lameness, collapse, regurgitation, drooling, ventroflexion of the head, and tremors. Megaesophagus is also commonly seen (presumably associated with the presence of striated muscle along the entire length of the esophagus in dogs), being as high as 88% in one survey [448]. Note that apart from fatigue/skeletal muscle weakness, neurological deficits may be minimal in some affected dogs [471]. In one study involving 1154 dogs, generalized MG was reported in 57% of cases [448]. Focal forms of MG have also been recognized in dogs, with an incidence ranging from 26% to 43% of all cases of MG [447,448,489]. Focal signs may include megaesophagus, pharyngeal paralysis and/or decreased palpebral reflexes, but without evidence of appendicular weakness [470,489-491]. Facial and laryngeal muscle weakness may also be observed. Focal MG in dogs may occur with thymoma [470]. Approximately 25% of dogs presented with idiopathic megaesophagus have increased serum titers of AChR-ab [489,492]. Idiopathic cardiac conduction disturbances (e.g., 3rd degree heart block) have been reported in some dogs with MG (with and without thymomas and with generalized and focal MG) [469]. A severe, fulminating form of MG has also been recognized in dogs clinically characterized by frequent regurgitation of large quantities of fluid associated with megaesophagus, rapid loss of muscle strength leading to recumbency that is not abated by rest, and marked respiratory distress [447,493]. Several of these dogs have had thymoma [493]. In a recent report involving 5 dogs with fulminating MG, titin and RyR antibodies were found [451]. In cats, signs often include progressive lameness, weakness, drooling and ventroflexion of the head [454,456,494]. Other signs may include head and body trembling (which may be related to exercise in some cats, but in others, it may be seen at rest), crouching posture, dysphagia, regurgitation, weight loss, and voice change. Megaesophagus/esophageal motility dysfunction may be present [454,495]. In a recent review of 105 cats with MG (diagnosis based on positive AChR-ab in serum samples), clinical data indicated that signs of generalized weakness without megaesophagus occurred in approximately 30% of cats, generalized weakness and megaesophagus/dysphagia occurred in 20%, generalized weakness associated with thymoma occurred in approximately 26%, while focal forms of MG, including megaesophagus and dysphagia, without signs of generalized weakness, occurred in approximately 15% of cats [444]. Some cats manifest stiff, choppy movements in all limbs, and after a few steps, they crouch to sternal recumbency and rest their heads on their forepaws. Many cats have facial weakness and are unable to close their eyelids (accompanied by lack of menace and absent palpebral reflex). Third eyelids may be protruded. Neurological examination may reveal normal sensation, intact tendon reflexes but diminished withdrawal reflexes, poor postural reactions, and proprioceptive deficits [455,457]. In human patients, MG has been classified into 4 grades: ocular disease (grade I), generalized weakness of mild (grade IIa) or moderate intensity (grade IIb), severe generalized disease (grade III), and fulminating disease/myasthenic crisis with respiratory failure (grade IV) [459]. Pathological findings (at the light microscopic level) in muscle are minimal but in our laboratory we have seen scattered angular, atrophic fibers in several muscle samples from dogs and cats with MG,

sometimes with small, focal aggregations of lymphocytic cells (lymphorrhages). Lymphocytic myositis has been reported/suspected in some affected dogs and cats with thymomas [456,466,469,496-498]. No changes are found in peripheral nerves. Immunocytochemical methods (e.g., staphylococcal protein A-horseradish peroxidase) may reveal presence of immune complexes localized at neuromuscular junctions [449]. Ultrastructural studies in human cases of MG indicate decreased number of acetylcholine receptors, widening of the synaptic space, and flattening of the regular undulations in the muscle cell membrane at the motor end-plate [460,461]. A significant reduction in muscle acetylcholine receptors has been shown biochemically in dogs with acquired MG [450]. Diagnosis is based on clinical signs, EDX evidence of decremental response of the compound muscle action potentials after repeated nerve stimulation (consistent with a postsynaptic transmission defect), serological testing for autoantibodies, and amelioration of signs following administration of the short-acting anticholinesterase edrophonium chloride (Tensilon), using a dosage of 0.1 - 0.2 mg/kg, IV in dogs and 0.25 - 0.5 mg IV in cats, total dose (anticholinesterase drugs inhibit the enzymatic elimination of acetylcholine, thereby increasing its concentration at the postsynaptic membrane). Neostigmine methylsulfate (Prostigmin) at 40 µg/kg, IM or 20 µg/kg IV may also be used in dogs. Following injection, an animal that has been previously recumbent may be restored immediately to normal activity, which will last for a few minutes before muscle weakness gradually returns. However, some dogs with MG may not respond, while dogs with other neuromuscular disorders may be responsive. It has been reported that the Tensilon test has not proven useful in the diagnosis of focal MG [489]. Note also that a decremental response to nerve stimulation is not always detected in dogs and cats with acquired MG [456,467]. Chest radiography, ultrasonography, or specialized imaging techniques (CT, MRI) may demonstrate a mediastinal thymic mass. EMG testing is normal, as is hematology, blood biochemistry, urinalysis and CSF analysis. Definitive diagnosis can be made using radioimmunoassays for detection of serum acetylcholine receptor antibodies that appear to be specific for acquired MG in dogs [475]. This test (a positive antibody titer in dogs is > 0.6 nmol/L; and > 0.3 nmol/L in cats) will detect nearly all cases of generalized MG [443]; lower serum titers reportedly occur in animals with the focal form of MG [489]. High serum AChR-ab titers were reported in dogs with acute fulminating MG [493]. It should be noted that the assay is not necessarily correlated to the severity of clinical signs in any affected animal, results may be negative in a small percentage of animals with generalized (<2%) or focal forms, and serum titers are decreased by immunosuppressive therapy >7 - 10 days [475,489]. Clinical improvement of signs may be associated with decreasing AChR-ab titers, and remission of signs may occur when titers reach < 0.6 nmol/L [489]. Recently, molecular cloning of the canine nicotinic acetylcholine receptor alpha- subunit gene has been reported along with development of an ELISA assay to facilitate diagnosis of MG in dogs [499]. In people, nearly all cases of MG can be diagnosed using a combination of tests, including AChR-ab titers, repetitive nerve stimulation studies, and single fiber EMG demonstration of increased "jitter" [459]. Prognosis is guarded, especially in dogs with thymoma [471]. Also, dogs with the acute fulminating form of MG appear to have a very guarded prognosis associated with propensity for developing aspiration pneumonia [493]. The presence of circulating RyR antibodies in dogs with various forms of MG may have negative prognostic significance (see above) [451]. Medical treatment usually entails a trial and error approach to the drug(s) used, dosage, frequency, or combination. Long-acting anticholinesterase drugs such as pyridostigmine bromide (Mestinon) may result in clinical control. Dosages range from 30 to 60 mg, PO, two or three times a day in dogs. Dosage depends on the severity of signs and on the size of the dog. In cats, oral pyridostigmine bromide syrup, starting at 2.5 mg bid, has been successful. Overdose in animals can produce a cholinergic crisis with signs of muscarinic (hypersalivation, lacrimation, urination, defecation, pupillary constriction, bradycardia respiratory paralysis), nicotinic (muscle fasciculations, tremors, stiff gait), or CNS (anxiety, hyperactivity, anorexia, generalized seizures) stimulation. Administration of atropine (at 0.2 - 0.4 mg/kg IV, slowly over 5 minutes) will reduce the muscarinic signs. Some animals with acquired MG may become refractory to anticholinesterase therapy after a period of successful treatment. However, Shelton and associates have recently reported spontaneous clinical and immunologic remission in 47 of 53 dogs treated only with anticholinesterase therapy (no immunosuppressive drugs were used) within an average of 6.4 months [475]. Interestingly, various neoplasms developed in the 6 remaining dogs that did not go into remission. It has been stated that anticholinesterases provide only symptomatic relief and have no effect on the underlying immunological dysfunction [500]. Accordingly, some cats have been treated aggressively with immunosuppressive doses of corticosteroids, e.g., prednisolone, 2 mg/kg, bid, for several months, followed by gradual reduction every 2 months over a 12 to 16 month period, has resulted in complete remission of signs and withdrawal of all therapy [455]. In some dogs and cats, combination of corticosteroids and anticholinesterases has been necessary [456,467]. In a report of acquired MG in a cat, successful management involved thymectomy in conjunction with long-term immunosuppressive corticosteroid therapy [457]. The efficacy of the corticosteroid treatment is probably related to both suppression of the immune response and to a direct facilitatory presynaptic action. One caveat is that corticosteroids may initially worsen clinical signs in some instances and steroid induced polydipsia can exacerbate the problem of regurgitation [471,475]. Azathioprine, alone or with pyridostigmine, has been used successfully to treat dogs with MG [501]. Another dog was successfully treated using plasmapheresis and corticosteroids [502]. In one report, surgical removal of a thymoma in a 10 year old mixed breed dog resulted in rapid remission of signs; however, the thymoma recurred 6 months post-operatively [470]. Treatment strategies in people with MG including anticholinesterase inhibitors (typically pyridostigmine), thymectomy, corticosteroids, cytotoxic agents (azathioprine, cyclosporine), plasma exchange, and intravenous pooled immune globulins have led to a low mortality rate and favorable prognosis for most patients (although lifelong immunomodulating therapy may be needed) [459]. It is recommended that the following drugs be avoided in animals

with MG (acquired or congenital) since they may further impair neuromuscular transmission [443]: aminoglycosides, phenothiazines, methoxyflurane, magnesium, and anti-arrhythmic agents.

**Congenital MG** in animals may occur as a postsynaptic or a presynaptic disorder. It has been described as a postsynaptic disorder in young dogs of several breeds: Jack Russell terrier [503,504], Springer Spaniel [505], and Smooth haired Fox terrier [506], usually appearing between the ages of 6 and 9 weeks, and with multiple cases occurring in a single litter. This form of congenital MG has also been reported in several cats, including a Siamese (5 month of age) and Domestic Shorthair cats (4 and 7 months of age) [453,507,508]. Congenital MG is inherited as an autosomal recessive trait in Jack Russell and Smooth haired Fox terriers [509,510]. The physiological basis of this form of congenital MG is the same as that of acquired MG; however anti-acetylcholine receptor antibodies are not demonstrable in serum or muscle in congenital MG. Ultrastructurally, there appears to be increased postsynaptic membrane density and shorter fold depths (possibly associated with abnormal trophic influences during synaptogenesis) [511]. Palmer and colleagues demonstrated a marked reduction in acetylcholine receptors (AChR) in skeletal muscle samples from Jack Russell terriers and Springer Spaniels with congenital MG [504,512]. In a related study, the low junctional membrane density of AChR in canine congenital MG was considered to represent a low insertion rate of AChR in the postsynaptic membrane rather than a primary inability of muscle to synthesize AChR, or an accelerated degradation of AChR in the postsynaptic membrane [513]. Clinical signs and electrophysiological findings of animals with postsynaptic congenital MG are similar to those described for acquired MG; however, signs of episodic weakness are often relentlessly progressive, ultimately leading to generalized weakness, muscle wasting and inability to ambulate, in spite of treatment. Megaesophagus has been observed only in the Smooth haired Fox terriers. Diagnosis is based on response to Tensilon (pyridostigmine bromide), using a dosage of 0.1 to 0.5 mg, IV. Mestinon (pyridostigmine bromide) is used for treatment at a dosage of 7.5 to 30 mg, PO, once daily. Clinical response to this drug is often erratic, with frequent relapses and animals may become refractory to treatment [504]. Accordingly, prognosis is guarded to poor in affected dogs. The prognosis of affected cats is uncertain because of insufficient numbers of reported cases; however, long-term treatment with pyridostigmine bromide syrup (1.5 mg, PO, bid) was beneficial in one cat [507]. Another congenital myasthenic disorder has been identified in Miniature Dachshund puppies around 5 - 6 weeks of age that is responsive to anticholinesterase therapy and resolves with maturation [443]. Presynaptic congenital MG has been reported in 12 to 16 week old Gammel Dansk Hønsehund dogs, with autosomal recessive inheritance [514]. Signs are characterized by exercise-induced weakness, short strides with flexed limbs, head drooping, occasional falling, and crawling movements. Muscle tone and reflexes are normal during attacks, there is no facial weakness, no swallowing defect, no megaesophagus, and no change in voice. The condition is not progressive and some dogs have been followed for 6 years. No antibodies to acetylcholine receptors are found. Anticholinesterase treatment has no effect on muscle weakness or electrophysiological changes. The underlying defect is considered to be presynaptic and may be due to a defect in the synthesis of acetylcholine, impaired release of acetylcholine, abnormality of acetylcholine-induced ion channels, or deficiency of end-plate acetylcholinesterase. Specific electrophysiological patterns may be used to identify heterozygotes as well as myasthenic dogs [515]. In humans, congenital MG is relatively rare and has been classified as presynaptic, synaptic (with end-plate acetylcholinesterase deficiency), or postsynaptic (consisting of abnormal function or numbers of acetylcholine receptors [516]. Inherited cases are usually associated with autosomal recessive inheritance.

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## **Neuropathic Disorders** (6-Feb-2003)

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### **Neuropathic Disorders**

The peripheral nervous system (PNS) comprises the cranial nerves, spinal nerve roots, dorsal root ganglia, the peripheral nerve trunks (motor and sensory nerves), the terminal branchings of motor nerves as they innervate skeletal muscle, and the peripheral autonomic system [1]. Disorders of the parent cell bodies located in the spinal cord (and/or brainstem) are discussed under motor neuron diseases. In people, dorsal root ganglion degenerations are described as sensory neuropathies, while in animals such disorders are sometimes called ganglionopathies or sensory neuronopathies. In the chapter on Localization, I have arbitrarily classified small animal neuropathies into hereditary/degenerative and developmental disorders, and acquired toxic, traumatic, metabolic, inflammatory/infectious, neoplastic/paraneoplastic, and vascular disorders (see neuropathic syndrome). Peripheral nerve disorders are common and usually well-recognized in dogs and cats, although in some instances problems may arise in distinguishing neuropathies from diffuse muscle disease, certain CNS disorders, or skeletal problems. In general, most acquired neuropathies are seen in both dogs and cats, although hereditary disorders are more commonly reported in dogs. Both sophisticated electrodiagnostic testing and qualitative/quantitative pathological studies have further defined peripheral nerve disease in small animals. Despite these advances, the etiology of many neuropathies in dogs and cats continues to be uncertain, in contrast with the situation in people, in whom approximately 10 to 15% of neuropathies remain cryptogenic [2].

The following neuropathic disorders will be described in this chapter and have been listed alphabetically:

#### **Alaskan Malamute Polyneuropathy**

#### **Birman Cat Distal Polyneuropathy**

#### **Brachial Plexus Avulsion**

#### **Brachial Plexus Neuropathy-neuritis**

#### **Congenital Hypomyelination Neuropathy**

#### **Dancing Doberman Disease**

#### **Deafness**

Congenital Sensorineural Deafness

Acquired Sensorineural Deafness

Normal Aging

#### **Diabetic Neuropathy**

#### **Distal Denervating Disease**

#### **Distal Symmetrical Polyneuropathy**

#### **Dysautonomia**

#### **Facial Paralysis**

#### **Familial German Shepherd Neuropathy**

#### **Giant Axonal Neuropathy**

#### **Hyperadrenocortical (Cushing's) Neuropathy**

#### **Hyperlipidemia**

#### **Hyperoxaluria**

#### **Hypertrophic Neuropathy**

#### **Hypoglycemic Neuropathy**

#### **Hypothyroid Neuropathy**

#### **Laryngeal Paralysis**

Laryngeal Paralysis Polyneuropathy Complex

#### **Optic Neuritis**

#### **Paraneoplastic Neuropathy**

#### **Peripheral Nerve Tumors**

#### **Polyradiculoneuritis**

Coonhound Paralysis

Idiopathic Polyradiculoneuritis

Cauda Equina Polyradiculoneuritis

Chronic Inflammatory Demyelinating Polyneuropathy

Infectious Polyradiculoneuritis

Postvaccinal Polyradiculoneuritis

Trigeminal Neuritis

#### **Rottweiler Distal Sensorimotor Polyneuropathy**

#### **Sensory Neuropathies**

Sensory Ganglioradiculitis

Progressive Axonopathy in Boxers

Sensory Neuropathy in Longhaired Dachshunds

Sensory Neuropathy in English Pointers

Sensory Trigeminal Neuropathy

Idiopathic Self-mutilation

#### **Storage Disease Neuropathies**

#### **Toxic Neuropathies**

#### **Traumatic Neuropathy**

#### **Vascular Neuropathy**

#### **Vestibular Disease**

Peripheral Vestibular Disease

- Idiopathic Vestibular Disease

- Otitis Media-interna

Cholesteatoma

- Congenital Vestibular Disease

- Miscellaneous Causes of Peripheral Vestibular Disease

Inflammatory Polyps

Central Vestibular Disease



### Abbreviations -

ADH (adrenal-dependent hyperadrenocorticism); ATPase (myofibrillar adenosine triphosphatase); BAER (brainstem auditory evoked response); CK (creatine kinase); CMAP (compound muscle action potential); CSF (cerebrospinal fluid); CNS (central nervous system); CT (computed tomography); EDX (electrodiagnostic); EMG (electromyography); HAC (hyperadrenocorticism); HSMN (hereditary sensory and motor neuropathy); MRI (magnetic resonance imaging); NADH-TR (reduced nicotinamide adenine dinucleotide tetrazolium reductase); NCV (nerve conduction velocity); PAS (periodic acid-Schiff); PDH (pituitary-dependent hyperadrenocorticism); PNS (peripheral nervous system); SSN (subacute sensory neuropathy)

### **Alaskan Malamute Polyneuropathy**

A progressive polyneuropathy has been reported in young mature Alaskan Malamutes [3]. Male and female dogs were affected and the mean age of onset of clinical signs was  $14.6 \pm 3.1$  months (range 10 to 18 months). Clinical signs included progressive paraparesis slowly progressing to thoracic limb weakness, incoordination with stumbling or toe-dragging, synchronous pelvic limb gait when running, exercise intolerance and collapse, inability to walk up stairs, inability to jump, difficulty standing, paraspinal (especially lumbar) or appendicular hyperesthesia, hyporeflexia, muscle atrophy (especially in distal limb muscles), proprioceptive deficits, and, in some cases, tetraplegia. A hoarse bark and/or inspiratory stridor were noted in 2 dogs. Electromyographic (EDX) testing revealed diffuse fibrillation potentials and positive sharp waves in limb muscles, especially in muscles below the elbow and stifle. Motor nerve conduction velocities were either normal or low-normal (50 to 60 m/sec) or slow (28 to 47 m/sec). Sensory NCV was normal in one dog tested. No decremental response to repetitive nerve stimulation was seen in one dog tested. Results of routine hematologic and blood biochemical analyses and thyrotropin response testing, blood lead concentration, serum cholinesterase activity, and immunologic function were normal. Ophthalmoscopy, spinal radiography, urinalysis, edrophonium testing were negative. Pathological findings in skeletal muscles included neurogenic muscle atrophy characterized by fiber size variation with atrophic/hypertrophic fibers, more frequent type 2 angular fiber atrophy, and fiber type grouping, without evidence of inflammation or antimuscle antibodies. In peripheral nerves, microscopic changes included focal or diffuse loss of myelinated nerve fibres, myelinoaxonal necrosis, increased endoneurial fibrosis, occasional infiltrating macrophages, and variable demyelination or remyelination. Axonal degeneration and nerve fiber loss were more prominent in distal parts of the nerves. Axonal degeneration was also noted in the sensory saphenous nerve. Ultrastructural changes included loss of myelinated fibers, axonal degeneration, presence of numerous Büngner bands, denervated Schwann cell subunits, collagen pockets, and occasional regenerating clusters. No onion-bulb formation was seen. Myelin debris, membranous bodies, and prominent organelles, especially mitochondria were observed in axons and Schwann cell cytoplasm. Macrophages were occasionally seen within Schwann cell cytoplasm of myelinated fibers containing degenerating axons. Some axons had a watery appearance with apparent loss of normal cytoskeletal components. There was no evidence of axonal neurofilamentous accumulation or tubovesicular aggregates. The nature and distribution of abnormal electrophysiological and pathological findings were suggestive of a distal sensorimotor polyneuropathy. Prognosis is guarded to poor since the disorder appears to be progressive in most dogs. Response to corticosteroids and azathioprine have been unsatisfactory. However, less clinically affected dogs may have a favorable prognosis and lead a reasonably normal life style (several dogs that we have followed are alive at 8 years of age). The cause of this condition remains obscure, although recessive inheritance is suspected. In a recent report from Germany, EDX and histopathological abnormalities were detected in clinically normal relatives of affected dogs [4]. Interestingly, abnormal vocalization was also noted in some affected dogs. Note that the signalment, age of onset, and clinical course of this disease are similar to those reported in Norwegian Alaskan Malamutes, a hereditary (autosomal recessive) polyneuropathy that was believed to have been eradicated in Norway in 1982 [5,6]. The Norwegian dogs had evidence of coughing, regurgitation, and megaesophagus, proximal and distal abnormalities on electrodiagnostic testing, atrophy of laryngeal muscles, primarily demyelinative changes in nerves at all levels (Dr. L. Moe, personal communication, 1997), and a guarded to favorable prognosis, often with clinical recurrences. It seems likely that these two conditions are manifestations of the same disorder, although we had initially suggested the term "idiopathic polyneuropathy of Alaskan Malamutes" to distinguish the present condition from the hereditary neuropathy of the Norwegian dogs [3]. Future studies should help clarify if these neuropathies are different expressions of the same disorder.

### **Birman Cat Distal Polyneuropathy**

A degenerative polyneuropathy has recently been reported in several litters of Birman cats bred from the same parents. A recessive mode of inheritance is suspected [7]. Pathologically, the central nervous system (CNS) lesions were most prominent in the lateral pyramidal tracts of the lumbar spinal cord, the fasciculi gracili of the dorsal column in the cervical spinal cord, and the cerebellar vermal white matter. Lesions were characterized by diffuse loss of myelinated fibers and fibrillary astrocytosis. Inflammatory changes were not seen. Neurons of the cerebral cortex, cerebellum, and brainstem were normal. In the PNS, numerous degenerating nerve fibers were observed in the sciatic nerves but not in the spinal nerve

roots. No changes were found in the cauda equina, dorsal root ganglia, or ventral horn cells. Ultrastructurally, degenerating ovoids consisting of myelin debris and disrupted axons were frequently observed. Selective involvement of distal portions of the CNS and PNS suggested that this disorder is a distal central-peripheral axonopathy (dying-back disease). Clinical signs were first noted in cats 8 to 10 weeks of age. Affected cats fell frequently and had a tendency to stand and walk on their hocks which were held in an adducted fashion. The gait was characterized by slight hypermetria in all limbs and there was progressive pelvic limb ataxia. Analysis of blood and CSF was normal. Nerve conduction velocity studies were normal; however, EMG revealed presence of fibrillation potentials and positive sharp waves in pelvic limbs. Prognosis is poor. Presently, there is no treatment. Future breeding trials should confirm that this condition is caused by a genetic defect and help characterize the exact mode of inheritance.

### Brachial Plexus Avulsion

The brachial plexus consists of the large nerve plexus which gives rise to the nerves which supply the thoracic limb. It is formed by the ventral branches of the 6th, 7th and 8th cervical and the 1st and 2nd thoracic spinal nerves [8-11]. Traumatic injury to the brachial plexus is often encountered clinically in animals, especially dogs, in which there is traction of the thoracic limb or severe abduction of the scapula. Typically, it is the nerve roots, not the plexus itself, that bear the brunt of traumatic avulsive injury because of the lower resistance of nerve roots to stretch (due to lack of a perineurium). The ventral roots are more susceptible to traumatic stretch than the dorsal roots. Avulsion is usually intradural and the lesion in dogs is diffuse rather than circumscribed with involvement of fibers at many different levels [12,13].

Degenerative changes in dorsal and ventral nerve roots and ventral branches of spinal nerves are characterized by axonal necrosis, myelin fragmentation, and loss of myelinated fibers. Many fibers are damaged where they penetrate the leptomeninges, resulting in neuroma formation. Retrograde changes are observed in the ventral horn cells, characterized by chromatolysis, cell swelling and neuronal depletion. Retraction balls may be seen. Dorsal column degeneration occurs only with lesions central to the dorsal root ganglion.

Clinical signs reflect the distribution of damage to nerve roots, branches, and plexal cords rather than direct peripheral nerve involvement. Signs may vary from weakness of single muscle groups, without sensory loss, to paralysis of all thoracic limb muscle groups with accompanying sensory loss (e.g., with a lesion from C6 to T1 - 2). A lesion that involves spinal cord segments C8 - T1 may produce ipsilateral loss of the panniculus reflex; while involvement of the T1 - 3 roots, which contains preganglionic sympathetic fibers, frequently results in partial Horner's syndrome (characterized by anisocoria). Patterns of cutaneous anesthesia associated with brachial plexus avulsions have been described in the dog [14]. Conscious pain presentation is usually impaired to a variable degree in all dogs with brachial plexus avulsion. In general, desensitized areas of skin may be detected on lateral, medial, dorsal, and palmar surfaces of the affected thoracic limb. Brachial plexus avulsion may be confused with radial paralysis since the clinical signs of avulsion are predominantly those of radial nerve paralysis at the level of the shoulder [15]. Table 1 outlines some differentiating features between these conditions.

<b>Table 1. Radial Nerve Paralysis Versus Brachial Plexus Avulsion.</b>		
	<b>Radial Nerve (C6 - T2)</b>	<b>Brachial Plexus ( C6 - T2)</b>
Level of injury	Radial nerve	Brachial plexus
Muscle atrophy	Triceps, carpal extensors	Any forelimb muscle
Sensory loss (skin)	Craniolateral forearm, dorsal paw	Any forelimb skin zone
Panniculus reflex	Present	± absent ipsilaterally
Horner's syndrome	No	± yes (often partial if present)

Modified from Braund KG. Clinical syndromes in veterinary neurology. St. Louis: Mosby, 1994 [16].

Diagnosis is most commonly based on historical and clinical data [17]. Electrodiagnostic (EDX) testing is useful for detecting muscle denervation, especially minor degrees which cannot be uncovered by routine neurological examination. This information may be helpful in those cases where muscle-tendon transposition is being considered for surgical management. Myelography may occasionally demonstrate a contrast-outlined diverticulum at the level of the cervicothoracic junction. More recent studies suggest a diagnostic and prognostic role for CT-myelography [18]. It has been

reported that exploration of the brachial plexus is not productive since the extent of the lesion cannot be determined at that level [19]. In general, the prognosis is guarded to poor. EDX testing will detect early changes in reinnervation and recovery. Some fibers, following acute injury, may show a temporary conduction block, from which they will recover within a few days. Since the roots of the radial nerve are commonly injured in brachial plexus avulsion, an electrodiagnostic evaluation of the radial nerve may provide early prognostic information: prognosis being poor in animals with initial, decreased radial nerve conduction velocity [19,509]. If this situation remains unchanged after 4 weeks, with concurrent severe EMG changes in the triceps muscle, there is virtually no chance of spontaneous recovery. In a recent study of prognostic factors in dogs with brachial plexus avulsion, the best predictor of complete recovery was pain perception, with 5 of 7 dogs with normal sensation recovering completely [509]. Muscle tendon transpositions have been successful in some dogs with partial avulsion. Carpal fusion may be useful in animals with adequate triceps muscle function that have a tendency to knuckle over on their paws [20]. Amputation of the affected limb may be necessary if the limb is severely excoriated from dragging or self-mutilation. Experimental studies in dogs suggest that ventral root reimplantation can successfully promote reinnervation [21,22]. Successful bypass coaptation procedures for cervical nerve root avulsion have been reported in people [23].

### **Brachial Plexus Neuropathy-Neuritis**

This is a rare, bilaterally symmetrical, neurological condition reported in dogs and cats that involves the nerves of the brachial plexus [24,25]. It has been suggested that this canine disorder may be the result of an allergic or hypersensitivity reaction similar to serum neuritis in man following prophylactic inoculations such as tetanus antiserum. The proposed pathogenesis is that the allergic condition produces spinal nerve swelling and subsequent compression at the level of the intervertebral foramina. In people, acute brachial plexus neuritis is an uncommon disorder characterized by severe shoulder and upper arm pain followed by marked upper arm weakness [26]. At least some forms are considered to represent an immuno-allergic mechanism [27,28]. Brachial plexus neuritis has also been recently reported in a man associated with herpes zoster [29].

Clinical signs described in a 9 month old Great Dane were characterized by acute onset of thoracic limb paresis with depressed or absent reflexes and hypotonia, facial paresis and neurogenic atrophy in all thoracic limb muscles. Pain perception appeared diminished over antebrachial regions. EMG studies revealed denervation potentials and absence of evoked muscle action potentials in the thoracic limbs. CSF evaluation was normal. Axonal degeneration was observed in a biopsy of a sensory branch of the radial nerve. This dog manifested two allergic episodes with facial edema and generalized urticaria over a 48 hour period prior to development of neurological signs. Immunological testing indicated that these signs were related to an all horse-meat diet. Three weeks prior to onset of signs the dog had been vaccinated with modified-live rabies virus. No improvement was noted in this dog 49 days after onset of clinical signs even with glucocorticoid therapy. Pathological findings include severe, asymmetrical axonal and myelin degeneration (characteristic of Wallerian degeneration) of peripheral nerves of the brachial plexus. The changes were most severe in the proximal ventral roots where there was axonal loss, variable axonal regenerating clusters, increased endoneurial fibrosis, many lipid-containing macrophages, and many endoneurial mast cells. Retrograde chromatolytic lesions were seen in the ventral horns cells of the cervical intumescence as well as in dorsal root ganglion cells. In a 1.5 year old Doberman Pinscher with brachial plexus neuropathy characterized by axonal degeneration, slight improvement was reported 4 months after signs first developed. No treatment was given. A milder form of brachial plexus neuropathy has been reported in several dogs presented with shifting thoracic limb lameness and diffuse EMG changes typical of denervation [20]. Myelography and CSF analysis were normal. Some of these dogs were steroid-responsive, while others clinically improved when fed poultry-based diets that contained no beef or horse products.

Brachial plexus neuropathy has been reported in a cat with clinical signs similar to those in the dog [30]. Reflexes in thoracic limbs were depressed and nerve conduction velocity was markedly reduced in the median nerve; however, EMG studies in thoracic limbs were normal. The cat recovered spontaneously over a three-week period. The neuropathy was thought to be causally related to vaccination with modified live rabies virus.

### **Congenital Hypomyelination Neuropathy**

In contrast with CNS hypomyelination, hypomyelination of the peripheral nerves is rare, but has been reported in two Golden Retriever littermates [31,32]. Both dogs were presented for pelvic limb ataxia at 7 week of age. Both had a crouched stance, mild pelvic limb atrophy, and weakness. Circumduction was evident in pelvic limbs when walking, and a bunny hop gait was present when running. Segmental spinal reflexes were depressed or absent in all limbs. Motor nerve conduction velocities were markedly reduced in sciatic-tibial and ulnar nerves. Needle EMG studies were normal except for rare denervation potentials in a few muscle groups. Teased nerve fibers were difficult to see because of lightness of myelin staining. Light and electron microscopic findings included reduced number of myelinated axons, presence of myelinated sheaths inappropriately thin for the calibre of the fiber, poor myelin compaction, increased numbers of Schwann cell nuclei, increased concentration of neurofilaments in myelinated axons, many Schwann cells with voluminous cytoplasm, and

increased perineurial collagen. Onion bulb formation was not seen and there was no evidence of demyelination. In contrast to controls, a poor correlation was seen between numbers of myelin lamellae (ML) and axonal circumference (AC). The frequency distribution of ML ranged from 5 to 55 lamellae in affected animals (mean, 28 lamellae) compared to 20 to 140 lamellae in controls (mean, 66 lamellae). The ML/AC ratio was reduced in nerves of affected dogs. Morphometric results indicated that fibres of all calibres were hypomyelinated. Axons appeared normal. Possible Schwann cell defect or abnormal axon-Schwann cell signaling were suggested to account for the hypomyelination [31]. The defect appears to be reversible since both dogs clinically improved. Repeat nerve biopsies around 2 years of age showed that myelination had increased, although it was still less than normal. Motor nerve conduction velocity studies also showed improvement, but were only about half normal values. Both affected dogs were able to live a normal life span.

The condition appears similar to the rare congenital hypomyelination neuropathy (CHN) in children [33]. CHN is a member of a heterogeneous group of hereditary demyelinating/dysmyelinating peripheral neuropathies that includes hereditary neuropathy with liability to pressure palsies (HNPP), Charcot - Marie - Tooth disease (CMT), and Dejerine-Sottas syndrome (DSS), all of which may represent a spectrum of related "myelinopathies" due to an underlying defect in myelination [34]. Some forms of CHN are associated with missense point mutations of PMP22 (peripheral myelin protein 22) leading to possible disruption of Schwann cell growth and differentiation [35,36]. CHN has also been identified in people with a mutation in the gene for protein zero (P0) [37].

Note that hypomyelination may also occur in various storage disorders. Using ultrastructural morphometric studies of G-ratios, we have recently identified universal hypomyelination in cats with alpha-mannosidosis [38] and in dogs with globoid leukodystrophy [39].

### **Dancing Doberman Disease**

Dancing Doberman disease (DDD) is a term given to a chronic, slowly progressive, neuromuscular disease that, to date, has only been described in Doberman Pinschers [40,41]. Recent studies suggest the condition is inherited as an autosomal recessive trait (Dr. Janet Steiss, Tuskegee University, unpublished data, 2002). DDD was originally regarded as being either a behavioral disorder or a sensory neuropathy [40], and later as a possible distal polyneuropathy [42]. Dogs of either gender, from 6 months to 7 years of age, initially manifest flexion of one pelvic limb when standing. Similar signs may be noted in the opposite pelvic limb several months later, and affected dogs begin to alternately flex and extend each pelvic limb in a dancing motion and prefer to sit rather than stand. The condition progresses insidiously over several years. There is apparent pelvic limb weakness, proprioceptive deficits, and gradual atrophy of pelvic limb musculature, especially the gastrocnemius muscles. Pelvic reflexes are normal or hyperactive. Affected dogs do not appear to be in pain based on subjective examination, including manipulation or palpation of the affected limb(s) or spine. Mild numbers of positive sharp waves and fibrillation potentials have been detected on EMG testing in some animals, primarily involving the gastrocnemius muscle(s). Bizarre high frequency discharges may develop after several years. Sensory and motor nerve conduction velocities are normal. Results of hematology, blood chemistries, serum creatine kinase levels, thyroid function testing, CSF analysis, and joint fluid examinations are within normal limits. Histopathologic changes in most muscles are minimal. However, changes are seen in the gastrocnemius muscle(s) including multifocal atrophy and hypertrophy, numerous fibers with internal nuclei, focal necrosis, endomysial/perimysial fibrosis, and sometimes, histochemical fiber type grouping. These changes resemble findings seen in adult canine myotonic myopathy. Reported nerve changes in older dogs are variable, but including demyelination and remyelination, and occasional axonal necrosis [41]. In samples from one 9 year old Doberman examined in my laboratory, the nature and incidence of neurogenic changes in several peripheral nerves and nerve roots were similar between left and right pelvic limbs and between proximal and distal samples, thus ruling against a distal neuropathy in this case. The incidence of changes was considered to be higher than those associated with normal aging. In another nerve biopsy examined in our laboratory from a 1 year old Doberman with clinical signs of Dancing Doberman disease, severe degenerative changes were seen that were dominated by axonal necrosis. In a recent study of DDD conducted at Scott-Ritchey Research Center, Auburn University College of Veterinary Medicine (Dr. Janet Steiss, Tuskegee University, unpublished data), degenerative changes were found in mixed, sensory, and sympathetic nerves suggesting either a sensorimotor autonomic neuropathy or possibly a sensory autonomic neuropathy. In this study, ultrastructural changes included myelinoaxonal necrosis and scattered presence of denervated Schwann cells involving myelinated and unmyelinated fibers. The proprioceptive deficits and mild or absent EMG changes in most muscles (with the exception of the gastrocnemius muscle) might suggest that DDD is a sensory neuropathy, with similarities to the rare hereditary sensory and autonomic neuropathies in humans (HSAN) [43]. In these conditions, there is selective involvement of the peripheral sensory and autonomic neurons, with axonal degeneration. The symptoms are related to which population of neurons is affected. In some types of HSAN, patients are afflicted with the abnormal sensation of burning soles or other forms of dysesthesia. Similar discomfort associated with pressure on the feet could account for the constant lifting of the feet in dogs with DDD. The changes in the gastrocnemius muscles from DDD dogs remain enigmatic and do not appear to be neurogenic, although there are instances in which myopathic-appearing lesions (e.g., rounded atrophic/hypertrophic with

central nuclei, fiber splitting, increased endomysial fibrosis, whorled, and fiber degeneration/regeneration) occur in primary neuropathies, e.g., Charcot - Marie - Tooth disease type 2, a form of hereditary sensory and motor neuropathy in people [44]. Perhaps the muscle changes reflect some form of reflex sympathetic dystrophy, a syndrome characterized by a triad of autonomic, motor, and sensory symptoms associated with abnormally increased sympathetic tone [45]. The presence of abnormal thermographic patterns seen in some affected dogs might be compatible with an imbalance between activity of sympathetic vasoconstrictor nerves supplying arteries and those supplying veins, potentially leading to muscle necrosis/atrophy [46]. Further studies should help clarify this confusing disorder.

At present, there is no treatment. Therapeutic trials using diazepam and primidone have not been effective. The long-term prognosis for a pain-free, acceptable pet is good [41]. To date, there have been no reports of spontaneous clinical improvement or resolution of signs in any affected dogs.

## **Deafness**

Deafness or hearing loss may be conductive, sensorineural, or central. In animals, as in humans, the most common type of deafness is sensorineural hearing loss associated with a lesion in the cochlear or eighth cranial nerve (see below).

Conductive deafness stems from problems within the external or middle ear cavities so that sound is not conducted into the inner ear. The most common cause of conductive deafness is chronic otitis externa-media, sometimes in association with cholesteatomas [47]. Other causes include external ear canal occlusion or ablation, atresia of the external acoustic meatus, rigidity or rupture of the tympanic membrane, damage to the ossicular chain (stapes, malleus and incus), or fluid within the middle ear [48,49]. Congenital palatine defects in dogs and cats may predispose to middle ear disease and hearing loss [50]. Conduction deafness has been noted in Scottish fold osteodystrophy [51]. Central hearing loss resulting from damage to CNS auditory pathways is rare in people and in animals. Central deafness has been noted in Labrador retrievers with spongy degeneration of the CNS [52]. In one study of deaf Dalmatian puppies, morphological abnormalities were found in the temporal lobes, medial geniculate bodies, acoustic tracts of the tectal surface, caudal colliculi, pons, medulla oblongata and trapezoid bodies, indicative of retarded development of the CNS (with a 40% reduction in the area of the acoustic cortex) [53].

Sensorineural deafness resulting from cochlear abnormalities may be congenital or hereditary, acquired due to ototoxic drugs or inflammatory diseases, or associated with normal aging.

Congenital sensorineural deafness is usually present from birth, or within a few weeks post-natally, and it is permanent. Some animals are affected unilaterally. The etiology of congenital deafness is unclear. Maternal exposure to ototoxic drugs, such as streptomycin, or viral infection has been suggested as a cause in some instances of congenital deafness [54]; however, the incidence of deafness from these causes is considered to be low [55]. Autosomal recessive disorders have been reported in Bull Terriers [56], Doberman Pinschers [57], and in colony Pointers selectively bred for excessive nervous behavior [58], and have been cited for Rottweilers and Pointers [55]. Congenital deafness is frequently associated with pigmentation disorders such as a white coat color and blue eyes [55,59-62]. Coat color abnormalities have been linked with the "merle" color gene. In heterozygotes, this dominant gene will increase the amount of white in the animal's coat, cause dappling in the pigmented portions of the coat, and also alter the pigment in the tapetum and iris. In the homozygous state the gene commonly produces a nearly all white animal that is deaf and blind. Congenital/hereditary deafness is frequently seen in blue-eyed white cats (transmitted as an autosomal dominant trait), Dalmatians, Australian Heelers, English Setters, Catahoulas, and Australian Shepherds. The Dalmatian reportedly has the highest prevalence of deafness of all canine breeds, with an overall incidence from 15 to 30% [54,63-65]. The condition in Dalmatians is consistent with an autosomal recessive, multifactorial gene with incomplete penetrance [66]. The deafness may be unilateral (most common) or bilateral. In a recent study involving > 3000 Dalmatians, an increased prevalence of deafness was found in females, especially in those with two blue eyes [67]. In this study, there was no difference in the prevalence of hearing loss between offspring of deaf mothers and the offspring of deaf sires.

Congenital deafness has been noted in numerous canine breeds (Old English Sheepdogs, Norwegian Dunkerhound, dappled Dachshund, Harlequin Great Dane, Shetland Sheepdog, Samoyed, Great Pyrenees, Sealyham Terrier, Greyhound, Beagle, Maltese Terrier, Bulldog, Boxer, Akita, American Staffordshire Terrier, Fox Terrier, Miniature Poodle, Papillon, Ibizan Hound, Kuvasz, Saint Bernard, Rhodesian Ridgeback, Scottish Terrier, West Highland White Terriers, Cocker Spaniels, Border Collies, Scotch Collies, Boston Terriers, Walker American Foxhounds, and Shropshire Terriers [55,68], but the mode of inheritance remains to be defined.

In animals with congenital deafness, pathological findings consist of total or partial agenesis of the organ of Corti, the spiral ganglion, and the cochlear nuclei [69-72]. Additionally, in congenitally deaf Collie and Dalmatian puppies, partial collapse of the saccule, atrophy of the saccular nerve and obliteration of the cochlear duct have been described [73]. Some forms of hereditary deafness are thought to be associated with cochleosaccular degeneration in which the stria vascularis is atrophic due to absence of normal pigment cells [55,72]. This leads to secondary degeneration of the organ of Corti, and collapse of the saccule. In a study of congenital deafness and vestibular disease in young Doberman Pinscher puppies, histopathologic

studies revealed that all affected puppies had a non-inflammatory neuroepithelial degeneration of the cochlea with a progressive loss of the auditory sensory hair cells, resulting in almost complete loss of the organ of Corti by 11 weeks of age [57].

Acquired sensorineural deafness can result from various ototoxic agents [74,75]:

1. Aminoglycoside antibiotics are the most common ototoxic drugs. These drugs concentrate in perilymph and endolymph, thus exposing the cochlear hair cells to high concentrations of the drugs (note that cochlear hair cell activity is dependent on endolymph fluid production by the stria vascularis). While all aminoglycoside antibiotics can damage auditory and vestibular receptors, streptomycin and gentomycin have their greatest effects on the vestibular system, whereas, neomycin, kanamycin, tobramycin, and amikacin sulfate produce more damage to the auditory peripheral receptors. The toxic effects of these drugs is believed to be heightened if the tympanic membrane is perforated. Experimental studies suggest enhanced ototoxicity with nutritional deficiency [76].
2. Other ototoxic antibiotics - topical polymixin B and chloramphenicol.
3. Antiseptic solutions - ethanol, iodine, iodophors, chlorhexidine, benzalkonium chloride, benzethonium chloride, and cetrimide. Chlorhexidine combined with cetrimide is especially toxic in dogs and cats. Interestingly, the use of 0.2% chlorhexidine acetate is reportedly safe when instilled into the external ear canals of normal dogs for a period of 3 weeks (and no signs of ototoxicity occurred in dogs with surgically perforated tympanic membranes) [77].
4. Diuretics - ethacrynic acid, bumetanide, and furosemide. These agents induce changes in the stria vascularis of the cochlear.
5. Antineoplastic agents - cisplatin, which acts on the hair cells in similar fashion to the aminoglycoside antibiotics.
6. Miscellaneous agents used in otic preparation - propylene glycol, ceruminolytic agents and detergents, especially if the tympanic membrane is ruptured.
7. Overdosage with closantel, a salicylanilide derivative, produced a reversible hearing loss in a dog [78].

Neuroepithelial degeneration, in which the organ of Corti is primarily affected, reportedly occurs mainly with acquired deafness [55]. Acquired sensorineural deafness occurred in a 3 year old Collie dog with disseminated protothecosis, in which *Prototheca* organisms disrupted the tectorial membrane and destroyed the organ of Corti [79]. Other causes of acquired sensorineural hearing loss in people include toxin exposure (e.g., high dose aspirin), Ménière's disease (paroxysmal symptoms of tinnitus, fluctuating hearing, monaural fullness, and episodic vertigo), and noise [80].

Normal Aging - Hearing impairment is also commonly noted in dogs with normal aging. The loss of ability to perceive or discriminate sounds associated with aging in people is termed "presbycusis". In one study, hearing loss in older dogs was associated with atrophy and loss of spiral ganglion neurons of the cochlea [81]. This loss of neurons and nerve fibers in the osseous spiral lamina was thought to be secondary to loss of hair cells and supporting cells in the organ of Corti. Similar changes have been previously reported in a 20 year old dog and in a 19 year old cat with progressive hearing loss [82]. While hearing is very difficult to assess accurately using response to sounds such as clapping, electrodiagnostic testing using the brainstem auditory evoked response (BAER) method (also known as auditory brainstem response) can provide early diagnosis of deafness, allowing breeders and owners to avoid propagating further affected litters [64,83-85]. The BAER is the only reliable method of identifying animals with unilateral hearing loss [86]. Bone conduction thresholds, using a bone vibrator against the head (e.g., mastoid process, mandible or zygomatic arch), can also be used to confirm conductive hearing impairment in the dog in the same way as in humans [87,88]. The ear canals open between 12 and 14 days in dogs and at 5 days after birth in cats. Mature hearing patterns are established by 30 to 40 days of age in dogs (e.g., 67Hz to 45kHz) and by 20 to 30 days in cats (e.g., 45Hz to > 64kHz) [55]. Deaf animals can be difficult to arouse from sleep, may be more aggressive than normal littermates, and may be very vocal. There is no treatment.

Deafness also has been reported in young dogs and cats accompanied by signs of peripheral vestibular disease. It has been seen in colony Beagles, Akita and Doberman Pinscher puppies, and Siamese kittens [89]. Clinical signs, which usually begin at 3 - 12 weeks of age, include head tilt, circling, and ataxia. Nystagmus is not a feature of this disorder, but there is a deficit in normal eye movements. With the exception of the Doberman Pinscher puppies in which severe degenerative lesions were found (see above), histopathologic lesions have not been reported. The vestibular signs are generally not progressive, and improvement is usually seen over a period of weeks or months. This is probably due to visual and somatosensory compensation rather than resolution of the problem. Deafness in these animals is usually permanent. In affected Doberman Pinschers (in which the disease is inherited as an autosomal recessive trait), hearing was absent in all puppies three weeks of age or older.

Prognosis in animals with hearing loss will vary according to the cause. Treatments are mainly focused on preventing further damage, e.g., avoidance of ototoxic medications in animals with mild sensorineural damage. Correction of causes of conductive deafness may be ameliorative. Hearing aids seem to work best in human patients with conductive deafness [80].

At this time, comprehensive trials evaluating hearing aids are lacking in dogs and cats with hearing loss. There is a recent report on surgical placement of a bone-anchored hearing aid in a dog with conductive deafness [90].

### **Diabetic Neuropathy**

Spontaneous diabetes mellitus is a well-recognized metabolic disorder in dogs and cats associated with impaired utilization of carbohydrates and enhanced lipid and protein use. Central nervous system effects of this metabolic condition relate to two hyperglycemic syndromes: diabetic ketoacidosis and nonketotic hyperosmolar hyperglycemia (see diabetes mellitus).

Diabetes mellitus may also be associated with peripheral nerve disease, with sporadic cases of spontaneous diabetic neuropathy reported in adult dogs and cats [91-98]. Recently, a retrospective study encompassed 19 cats with spontaneously-occurring diabetes neuropathy [519].

Clinical signs of diabetic neuropathy are extremely variable ranging from an insidious subclinical condition to one with an acute or chronic onset of weakness, progressive paraparesis, proprioceptive deficits, muscle atrophy and depressed spinal reflexes. Cats often assume a plantigrade posture in pelvic limbs. Lumbosacral hyperesthesia has been noted in affected dogs and cats [93,94,96]. Diabetic cataracts may be present. Hypotension has been documented in a dog with diabetic neuropathy [94].

Electrodiagnostic (EDX) testing has revealed fibrillation potentials, positive sharp waves and fasciculation potentials in muscles, decreased motor and sensory nerve conduction velocities, and decreased amplitudes of evoked compound muscle action potentials (CMAPs). Temporal dispersion/diminished amplitude of CMAPs evoked by stimulation at the hip, as compared with potentials evoked by stimulation at the hock [94,99], suggest conduction block. Rarely, bizarre-high frequency discharges (myotonic-like) have been recorded in dogs with clinical/subclinical diabetic neuropathy [94,99]. In the cat retrospective study, EMG abnormalities were mainly restricted to the most severely affected cases [519].

Pathological findings reported in dogs and cats range from active axonal degeneration to demyelination-remyelination and axonal regeneration, along with neurogenic skeletal muscle fiber atrophy [91,93,96,100]. In a 8 year old female Doberman Pinscher with diabetic neuropathy, axonal degeneration was the dominant finding (involving approximately 35 to 40% of teased nerve fibers) in biopsies of lateral and medial plantar nerves [93]. In one teased nerve fiber study involving diabetic dogs without signs of clinical neuropathy, the dominant lesions were demyelination, remyelination, and less prominent axonal degeneration and teased nerve fibers with evidence of axonal regeneration [91]. Semi-thin sections revealed scattered thinly myelinated fibers and regenerating clusters of myelinated fibers. Early onion-bulb formation was seen ultrastructurally. Morphometric analysis revealed that the changes occurred in larger-caliber fibers from distal plantar nerves but not in more proximal tibial nerves. The results of this study, and the EDX testing of these dogs [99], suggest that some forms of diabetic neuropathy in dogs (and cats?) reflect a distal polyneuropathy that involves motor and sensory nerves.

Diagnosis is based on laboratory evidence of diabetes mellitus (hyperglycemia, glycosuria, insulin assays) and clinical, neurological, electrophysiological, and nerve biopsy data. EDX testing is a useful non-invasive technique for detecting animals with subclinical diabetic neuropathy [99]. Prognosis is guarded; however, partial or full recovery can occur with good diabetic control from insulin therapy [93,94,96]. A high fibre diet has been shown to significantly improve glycemic control and quality of life in dogs with diabetes mellitus [528]. Preliminary studies suggest that sulindac (a substituted indene acetic acid) may ameliorate some histological abnormalities in experimental diabetic dogs [527].

We have observed a polyneuropathy (dominated by axonal degeneration) in a diabetic 4 month old Chow Chow puppy with pancreatic islet cell hypoplasia in which there was absence of delta cells, and diminished numbers of alpha and beta cells [101]. We have also seen degenerative changes in nerves from young Keeshonds with inherited diabetes mellitus (K.G. Braund and J.W. Kramer JW, unpublished data). Prognosis is guarded. At present, there is no effective treatment for the diabetic neuropathy; however adequate and long-term dietary and insulin control of the hyperglycemia can result in marked clinical improvement [93,102].

In people, a variety of PNS disorders may be seen with diabetes, including focal disorders (focal myopathies and mononeuropathies, often associated with injections and entrapment/compression/infarction, respectively), segmental disorders such as diabetic polyradiculoneuropathy, and generalized neuropathies such as diabetic distal symmetrical sensorimotor polyneuropathy (DDSPN) and diabetic autonomic neuropathy [103]. Diabetic autonomic neuropathy often occurs as a continuum of the symmetrical polyneuropathy [104]. DDSPN is the most common form and its glove-stocking distribution of paresthesia and numbness, the distal to proximal gradient of EDX abnormalities, and predominantly axonal involvement (especially of large myelinated fibers) are consistent with a dying-back neuropathy [105], while autonomic involvement leads to a various dysautonomic signs, including hypotension, pupillary miosis, and constipation. One characteristic pathological feature of diabetic nerves is hyalinization of endoneurial microvessels, typically associated with reduplication and thickening of microvascular basement membranes, and perineurial cells may have a thickened basal lamina [106,107]. Recent studies have also demonstrated significant abnormalities of the perineurium in the spontaneously diabetic dog (total perineurial sheath thickness, mean perineurial lamellar width, total interlamellar space, and perineurial cell basement membrane thickness [108]). Endoneurial capillary basement membrane area was significantly increased in

experimentally-induced (alloxan/streptozotocin) diabetic dogs [527], similar to that found in diabetic people. In this report, there was no loss of capillaries.

The pathogenesis of diabetic neuropathy remains unknown, although interaction of multiple factors is considered likely [109-111], including interactions between vascular factors (decreased nerve perfusion/endoneurial hypoxia, changes in endoneurial microvasculature) and metabolic factors (hyperglycemia, enhanced glycation end product formation, intraneural polyol pathway activation, protein C activation, and omega-6 essential fatty acid dysmetabolism) [112,113]. One study in diabetic cats demonstrated evidence of polyol pathway activity (marked increases in nerve fructose without appreciable sorbitol accumulation) [519]. Deficiency of several neurotrophic factors, namely nerve growth factor, neurotrophin-3, and insulin-like growth factors have also been implicated in diabetic neuropathy [114,115]. Preliminary clinical trials have demonstrated improvement in signs and symptoms of sensory neuropathy in human patients with lower extremity vascular occlusive disease after intramuscular injection of naked DNA encoding vascular endothelial growth factor [116], although it is uncertain if these positive effects result from an angiogenic activity (formation of new blood vessels) or a direct neurotrophic effect [117]. Inflammatory cell infiltrates in nerves of diabetic people (particularly in those with diabetic autonomic neuropathy) also suggests that inflammatory or immune mechanisms may be involved [110]. While axonal degeneration appear to be the dominant pathology in patients with DDSPN, it remains to be determined if the myelin changes are secondary to an axonopathy or develop from a primary schwannopathy [105]. Note that insulin deficiency is probably not related to the diabetic neuropathy since nerves (just as the CNS) are not dependent on insulin for glucose uptake/energy utilization [118].

### **Distal Denervating Disease**

This degenerative neuropathy is reportedly the most common canine polyneuropathy in the United Kingdom [119,120], but has not been reported elsewhere. In this disorder there is no breed, sex, or age predisposition. The etiology and pathogenesis are presently unknown. Affected animals have had no history of exposure to toxins. The rate of onset of clinical signs is variable from 1 week to greater than 1 month. The main presenting sign reported is tetraparesis. In some dogs, the head and neck cannot be supported and there is loss of voice. Mastication, swallowing, respiration and bladder function are unimpaired. Pain sensation is preserved. Muscle atrophy may be prominent, especially involving proximal extensor muscles. There is hypotonia and depressed or absent patellar reflexes. Facial nerve dysfunction has been observed. Moderate to marked spontaneous potentials (fibrillations and positive sharp waves) are present in limb, paraspinal, masticatory muscles, and tongue. Motor nerve conduction velocities are in the low-normal range. The amplitude of evoked potentials is reduced. Sensory nerve potentials are normal. Pathologically, there is degeneration of the distal intramuscular axons with collateral sprouting. Skeletal muscle changes are typical of neurogenic atrophy. Proximal and middle portions of peripheral nerves are normal, and there is no evidence of sensory nerve damage. The prognosis for full recovery is good, with appropriate nursing care. Most dogs recover spontaneously within 4 to 6 weeks of onset of clinical signs. Recurrence has not been reported. The condition is clinically similar to Coonhound paralysis and idiopathic polyradiculoneuritis, although the later diseases tend to run a more acute course.

### **Distal Symmetrical Polyneuropathy**

A distal symmetric sensorimotor polyneuropathy has been reported in young adult Great Danes (1.5 to 5 years) [121,122]. The cause and pathogenesis are not known; however, an inherited dying-back process of peripheral axonopathy has been suggested. Clinical signs include chronic pelvic limb paresis that progresses to involve thoracic limbs, and bilateral atrophy of head (masticatory) and distal limb muscles. A reduced response to painful stimuli has been observed. Electrodiagnostic studies reveal fibrillation potentials, positive sharp waves in distal limb muscles (below stifle and elbow), and absence of evoked muscle action potentials. Diagnosis is based on clinical, electrodiagnostic, and nerve biopsy data. Prognosis is poor. Affected dogs have shown no response to corticosteroids or thyroid hormone supplementation. Results of pathological and morphometric studies of peripheral nerves reveal myelinated nerve fiber degeneration and loss, especially of larger-caliber fibers, which are accentuated in distal parts of appendicular and laryngeal nerves. Varying degrees of demyelination and remyelination may also be present. Sensory and autonomic nerves are affected to a lesser degree. No lesions are found in the CNS.

In a 3 year old, male Setter-cross, an almost identical polyneuropathy was noted after canine heartworm disease therapy (thiacetarsamide), which was complicated by disseminated intravascular coagulation [123]. Indeed, it now seems that this polyneuropathy is not specific for Great Danes, since we have seen similar clinical signs and pathology in several other large-breed dogs, including Chesapeake Bay Retriever, St. Bernard, Newfoundland, Collie, Labrador Retriever, and Rottweiler (see Rottweiler Sensorimotor Polyneuropathy). Treatment, including corticosteroids, has been disappointing in dogs with distal symmetrical polyneuropathies; however, results of a recent therapeutic trial using prosaptide TX14(A), a homologue of a neurotrophic peptide sequence within the lysosomal protein saponin C, indicated promising beneficial clinical and pathological effects in some dogs [512].



## **Dysautonomia**

This disease has been frequently reported in cats [124-134] and dogs [129,135-142]. It was first reported in cats by Key and Gaskell [124] in the United Kingdom, where it is still mainly restricted, although it now appears to have a world-wide distribution [143]. It is much less common in the United Kingdom today than it was in the 1980's, although there have been recent outbreaks in closed cat colonies [144,145]. The etiopathogenesis of this disease is unknown. Immunological studies in affected cats have revealed no abnormalities [146]. In one study, there was no consistent factor identified when management, vaccinal status, and drug therapy were examined [147]. Attempts to transmit the disease have been unsuccessful. However, recent demonstration of antibodies against the nicotinic ganglion acetylcholine receptor in some dogs with dysautonomia (as also found in human patients [513]) suggests a possible autoimmune basis for this disease [514].

The condition has been reported in cats from 6 weeks to 11 years of age. In the majority of cases, clinical signs develop in less than 48 hours, but may take up to 7 days. Historically, cats begin vomiting/retching and become depressed and anorexic. The third eyelid protrudes, pupils are dilated and poorly responsive to light stimulation (but usually responsive to pilocarpine), and lacrimation is reduced. Cats may be febrile, emaciated, constipated (sometimes with fecal impaction) and dehydrated. Urinary and fecal incontinence may develop. Sneezing may occur and the nose is often dry. Dried exudate may block the external nares. Occasionally, very mild posterior ataxia or more generalized paresis, depressed proprioception, and absent anal reflex have been detected. Many cats have bradycardia of less than 120 beats/minute. Some animals manifest transient syncopal episodes. A clinical grading system has been proposed [148]. Megaesophagus is often present and is usually associated with regurgitation. The putative role of the parasympathetic system in the development of the megaesophagus appears somewhat complicated. This sign usually occurs with damage to the special visceral efferent system emanating from the solitary tract/nucleus [149]. The parasympathetic vagal nucleus gives rise to the general visceral efferent (GVE) axons that innervate the smooth muscle of the digestive system, and while experimental lesions of the parasympathetic nucleus reportedly cause esophageal paralysis in cats, it has been suggested that the GVE vagal neurons are not critical for direct initiation of smooth muscle activity in the digestive tract since intestinal peristalsis and colonic mass movement are maintained by intrinsic neural mechanisms [149].

Dysautonomia in dogs is common in parts of the United States [142], especially around SW Missouri, NE Oklahoma, and Eastern Kansas. More than 50 canine cases have been confirmed at the University of Missouri (Dr. Dennis O'Brien, University of Missouri; personal communication, 2000). Recently, the condition was diagnosed in a family of German Shorthaired Pointers (the dam and 4 of 5 puppies) [150]. In dogs, signs may be non-specific [151]: lethargy, depression, anorexia, retching, regurgitation, vomiting, salivation, constipation, or more commonly, diarrhea. Other signs include dry crusty nose, dry oral mucous membranes, subnormal Schirmer tear tests, dilated or anisocoric pupils (poorly responsive to light), prolapsed nictitating membranes, megaesophagus, decreased anal tone, and distended incontinent urinary bladder. Heart rate is often < 120 beats/minute (even after exercise), and neurological abnormalities such as twitching jaw muscles, cervical hyperesthesia, dilated anal sphincter, and decreased patellar reflexes have been observed sporadically. Affected dogs of different breeds have ranged in age from 4 weeks to 5 years.

Diagnosis may be facilitated by ocular pharmacological testing to confirm post-ganglionic sympathetic and parasympathetic dysfunction [127,131,142,148]. For example, rapid pupillary constriction following instillation of 0.1 to 0.05 % pilocarpine into the eyes of affected animals is suggestive of denervation hypersensitivity [127]. Decreased urinary catecholamine measurements (e.g., catecholamines and catecholamine metabolites, metanephrine and vanillylmandelic acid) are indicative of sympathetic failure and may be another useful diagnostic tool [127,152]. The bradycardia typically is unaffected by administration of anticholinergic drugs, such as atropine.

While many of the clinical signs (e.g., dry mucous membranes, mydriasis, regurgitation/constipation) suggest involvement of the parasympathetic nervous system (although bradycardia reflects sympathetic involvement) [153], the pathology primarily involves neuronal perikarya especially of autonomic ganglia, both sympathetic and parasympathetic [125,126,153,154]. Note that some signs, such as proprioceptive deficits and anal sphincter dysfunction, are non-autonomic. Lesions are characterized by chromatolytic changes in autonomic neurons (with loss of Nissl substance and eccentric/pyknotic nuclei), neuronal degeneration and loss, neuronophagia, and occasionally mild mononuclear perivascular cuffing (in one report, the majority of mononuclear cells were T lymphocytes [140]). In another report, 2 of the least affected cats had evidence of eosinophilic polymorphonuclear cells in several autonomic ganglia [144]. Ultrastructurally, there are dilated cisternae of rough endoplasmic reticulum, loss of Golgi complex, and large stacks of smooth parallel membranes which suggest possible disruption of neuronal glycoprotein biosynthesis [155,156]. In a dog with dysautonomia, numerous multilamellated bodies and myelin figures were seen in neuronal cytoplasm [137]. Degeneration has been found in many autonomic nerves with variable changes in myelinated and unmyelinated axons, including increased numbers of microtubules, which can be misaligned, vesicles, and branched vesiculotubular arrays of smooth endoplasmic reticulum. Changes are also frequently present in dorsal nucleus of the vagus and motor nuclei of cranial nerves III, V, VI, VII, and XII, ventral horn cells, and intermediolateral gray matter of spinal cord [140]. Note that degenerative changes (axonal

degeneration, demyelination) may also be found in peripheral somatic nerves (e.g., common peroneal nerve) of dogs and cats. In cats, enteric neurons are also affected based on reported depletion of immunoreactivity for vasoactive intestinal polypeptide, met-enkephalin, and substance P in peptidergic neurons throughout the gastrointestinal tract [148]. Sensory ganglia (e.g., dorsal root ganglia and ganglia of cranial nerves) are affected to a much lesser degree. The pathology has features in common with grass sickness of horses.

No specific treatment is available but supportive therapy is indicated and can be successful [132,157]. One review recommends correction of hypovolemia, hypothermia, hypoglycemia, and other electrolyte abnormalities; metoclopramide for vomiting and enhanced gastrointestinal motility; bladder evacuation (e.g., manually and/or with bethanechol); enemas for constipation; and total parenteral nutrition or tube gastrostomy for long-term alimentation [148,158]. Ophthalmic administration of parasympathomimetic drugs (e.g., 0.25 to 1.0 % pilocarpine) may stimulate lacrimal and oral secretions [157]; however, repetitious vomiting/regurgitation may become a complication [127]. Prognosis in dogs and cats is guarded to poor [158], especially in animals that suffer from persistent regurgitation/vomiting with heightened risk of inhalation pneumonia [148,151]. In one study, 28 of 40 cats did not survive the illness [154]. Cats that begin to produce secretions and eat and drink have the best prognosis. Clinical recovery may take up to 12 months. In affected dogs, mortality may exceed 90% [142,158].

In people, autonomic nervous system disorders may be associated with (a) diffuse autonomic failure (pandysautonomia), subcategorized into preganglionic, ganglionic/postganglionic, and peripheral neuropathies/neuronopathies with autonomic failure, and (b) those related to pure cholinergic or adrenergic disorders [159].

### **Facial Paralysis**

Idiopathic facial nerve paralysis of acute onset has been reported in mature dogs and cats (e.g., > 5 years). There is an apparent predisposition for Cocker Spaniels, Pembroke Welsh Corgis, Boxers, English Setters, and Domestic Longhair cats [160,161]. The cause of this condition is unknown. The facial paralysis is unrelated to otitis media. In one study of 95 dogs and cats with facial paralysis, the condition was considered to be idiopathic in 75% of dogs and 25% of cats [161]. Clinical signs are characterized by ear drooping, lip commissural paralysis, sialosis, deviation of the nose away from the affected side, and collection of food on the paralyzed side of the mouth. Menace response testing and palpebral reflexes are absent. Facial paralysis may be bilateral in some animals. There is no evidence of Horner's syndrome in animals with idiopathic facial paralysis. Electrodiagnostic testing may reveal spontaneous denervation potentials (e.g., fibrillations potentials and positive sharp waves) in superficial facial muscles. Stimulation of the facial nerve external to the stylomastoid foramen may fail to evoke muscle action potentials. Skull radiographic/imaging studies are usually non-contributory. Pathological studies of facial nerve biopsies may reveal active degeneration of large- and small-caliber myelinated fibers [160,162]. Inflammation has not been reported. Ultrastructurally, numerous macrophages may be present along with ovoids, Schwann cell proliferation, collateral sprouting, and various stages of remyelination. Prognosis is guarded. Improvement may take place in a few weeks or months, or may never occur. Chronic lip paralysis may result in permanent contracture, and the inability to close the eyelids often leads to corneal lesions due to lack of lacrimal lubrication. In one study, dogs with facial paralysis were ten times more likely to develop keratoconjunctivitis sicca, possibly as a result of damage to the parasympathetic preganglionic neurons within the facial nerve that pass to the lacrimal gland [161] (note that these parasympathetic fibers leave the facial nerve at the level of the inner ear, so decreased tear secretion will indicate a facial nerve lesion between the medulla and the middle ear [149]). Artificial tears may assist with corneal dryness. In a recent report of idiopathic facial paralysis of 35 days duration in a 7 year old female Yorkshire Terrier, acupuncture treatments (every other day for the first week, then once a week for the next 3 weeks) resulted in complete facial symmetry, normal ear movement and sensation, and voluntary closure of the eyelids [163].

In people, up to 75% of all cases of facial paralysis are also of unknown etiology and are called Bell's palsy [164]. High risk patients include those with diabetes mellitus or multiple sclerosis, and pregnant women [165]. Present knowledge suggests that Bell's palsy is most likely caused by herpes simplex infection and administration of acyclovir and corticosteroids facilitates recovery in most patients [166].

Acquired unilateral or bilateral facial paresis or paralysis in animals has also been seen in association with myriad disorders including polyradiculoneuritis (e.g., Coonhound paralysis), hypothyroidism, insulinomas, laryngeal paralysis-polyneuropathy complex, myasthenia gravis, botulism, middle ear infection/neoplasia, paraneoplasia, borreliosis, trauma external to the stylomastoid foramen (e.g., compression of the superficial branches of the facial nerve in anesthetized animals that have been lying in lateral recumbency for prolonged periods of time), extracranial tumors, or in conjunction with petrosal bone fracture [149,167-175]. Peripheral and/or central facial paralysis may be seen with brainstem inflammation or neoplasia (including pituitary tumors), and cerebral ischemia associated with parasitic migration [149,176-179]. It may occur secondary to surgical ablation of the external ear canal or bulla osteotomy for chronic otitis externa-media [180-185]. Intermittent facial spasms have been seen in dogs with idiopathic facial paralysis [161] and chronic otitis media [186], and may occur in animals with central brainstem lesions [187], presumably associated with increased

irritability of the facial nerve or facial nucleus. Facial twitching was seen in a cat with a pancreatic endocrine tumor (insulinoma), removal of which resulted in clinical remission [188]. Idiopathic paradoxical lacrimation ("crocodile tears") reported in a cat may have resulted from prior facial nerve paralysis affecting autonomic innervation [189]. In people, this condition (also known as Bogorad's syndrome) may follow facial palsy and is thought to result from aberrant migration of regenerating preganglionic parasympathetic fibers to the pterygopalatine ganglion rather than to the submandibular ganglion. Consequently during meals, stimulus for salivation results in stimulation of the lacrimal gland and increased tearing [165].

### **Familial German Shepherd Neuropathy**

A familial neuropathy has been reported in three older (10 years of age) German Shepherd dogs (one male, two females) that were littermates [190]. Progressive clinical signs, beginning around 9 years of age, included unsteady hind limb gait, tetraparesis, marked hind limb muscle atrophy, and depressed reflexes. Serological studies showed marked elevation in total lipids, CK levels, lactic dehydrogenase, and moderate decrease in aspartate aminotransferase concentration. Grossly, the sciatic nerves appeared swollen and fibrotic in two of the dogs. Microscopic changes in nerves included marked endoneurial fibrosis, loss of myelinated fibers, regenerating clusters, and numerous thinly myelinated axons. Active axonal degeneration was also seen, along with evidence of segmental demyelination/remyelination. No lesions were found in trigeminal and vagosympathetic nerves. Neurogenic muscle atrophy was observed in skeletal muscles (especially hind limb and paraspinal muscles) characterized by muscle atrophy/hypertrophy, endomysial fibrosis, fatty infiltration, mild regeneration, and histochemical fiber type grouping. Collateral ramifications/sprouting and multiple terminal arborizations were noted in terminal axons entering muscle. Based on these findings, the disorder was considered to represent an axonopathy with a dying-back pattern. Absence of onion-bulbs and the axonal lesions in these older dogs also suggested similarities to HSMN type II neuropathy in people, a usually dominant (sporadic and recessive cases are less commonly seen), distal axonopathy characterized by diffuse loss of larger-caliber myelinated fibers, little or no active degeneration, and prominent cluster formation [105].

The familial nature of this late-onset German Shepherd disorder is enhanced by the reported involvement of two other littermates (with less severe clinical signs), and the history that similar signs occurred in the mother and grandmother.

### **Giant Axonal Neuropathy**

Giant axonal neuropathy (GAN) is a rare inherited (autosomal recessive) neurological disease of German Shepherd dogs [191,192]. The pathogenesis of GAN is unknown, however it may represent a genetic defect in slow axonal transport affecting a wide variety of intermediate filaments [120], or altered neurofilament configuration [193,194]. An inborn error of metabolism of enzyme-linked sulfhydryl containing proteins, leading to impaired production of energy needed for normal organization of intermediate filaments has been proposed in human patients with GAN [195]. The neurofilaments in dogs with GAN have a normal polypeptide composition [196] and are morphologically similar to those seen in human GAN. In dogs, neurological signs are noted around 14 to 16 months of age, are more obvious in pelvic limbs, and are progressive. Signs are characterized by paresis, proprioceptive loss, diminished patellar reflexes, and pelvic limb hypotonia with atrophy of muscles below the stifles. Conscious perception of pain is gradually reduced in pelvic limbs. Bark may be lost or diminished and there may be fecal incontinence. Megaesophagus develops around 18 months resulting in regurgitation and occasional inhalation pneumonia. By 18 to 24 months of age, tetraparesis is pronounced. Note that affected dogs often have a very tight curl of their hair coats [193] (kinky/curly hair is a characteristic finding in children with GAN). Electrophysiologically, amplitudes of evoked compound muscle action potentials are decreased several months prior to clinical evidence of neuropathy [192,193]. This decrease is progressive. Denervation potentials are demonstrated by EMG in distal muscles of pelvic and thoracic limbs by 18 months of age.

Pathologically, the disease is characterized by loss of myelinated nerve fibers and presence of giant axons in myelinated and unmyelinated fibers [197-199]. Myenteric and distal vagal axons are also affected. The swollen axons contain masses of disordered 10 nm neurofilaments in both nodal and paranodal locations. Axonal collections of paracrystalline structures may also be seen in canine and human GAN nerves [194]. Similar morphological changes are found in the CNS with axonal swellings found in the distal portions of the spinal long tracts (e.g., caudal lumbar segments and rostral cervical segments) and their terminations in the cerebellar vermis, in the distal optic pathways, nuclei of the habenulo - interpeduncular tract, various thalamic relay nuclei, and the cerebral cortex [191,198,199]. Other organelles that may accumulate include mitochondria, membranous bodies, glycogen bodies, amorphous electron dense material, and occasionally, smooth endoplasmic reticulum [199]. Adjacent astrocytic processes may be enlarged with excessive whorling of the glial filaments. Attenuation of the myelin sheath over the swellings is seen in the PNS and CNS. The predominance of lesions in both PNS and CNS at the distal ends of large motor and sensory nerve fibers suggests that the disease represents a central-peripheral, distal axonopathy [191,192,198]. Similar lesions are seen in experimental studies of various neurotoxins, including acrylamide, IDPN, n-hexane, and methyl-n-butyl ketone [200]; however, the axonal neurofilamentous accumulations in

human and canine GAN differ from those seen with 2,5-hexanedione neuropathy [194].

Diagnosis is based on signalment, clinical, electrodiagnostic, and pathological (nerve biopsy) data. Prognosis is poor. There is no treatment.

### **Hyperadrenocortical (Cushing's) Neuropathy**

In our laboratory, we have found evidence of a peripheral neuropathy in several dogs with hyperadrenocorticism. Changes have included demyelination, remyelination, occasional axonal degeneration, and neurogenic atrophy in muscle, sometimes accompanied by signs of reinnervation (fiber type grouping). These changes have been observed in dogs with and without histopathological evidence of hyperadrenocortical (Cushing's) myopathy. Electrodiagnostic changes may include fibrillation potentials and positive sharp waves, along with significantly slowed nerve conduction velocities [515].

### **Hyperlipidemia**

Hyperlipidemia is defined as an excess of blood lipids, and as most lipids in blood are incorporated into lipoproteins and transported by these particles, the condition is also called hyperlipoproteinemia [201]. Lipoproteins may be separated into four major classes: chylomicrons, very low-density lipoproteins, low-density lipoproteins, and high-density lipoproteins [201-203]. Chylomicrons and very low-density lipoproteins are involved primarily in triglyceride transport, while low-density lipoproteins and high-density lipoproteins are involved with cholesterol transport [204]. Chylomicrons are composed predominantly of triglyceride and are cleared from the plasma by lipoprotein lipase and its cofactor, apoprotein C-II (apo C-II). Removal of triglyceride from the core of the chylomicron leaves a cholesterol-rich remnant particle that is removed from the circulation by the liver [201,202,205]. Lipid disorders infrequently involve the nervous system in dogs and cats, with the notable exception of hyperchylomicronemia, a familial condition in cats that is characterized by fasting hyperchylomicronemia. This lipid disorder appears to have a world-wide distribution, with reports from New Zealand, United States, and Europe [206-209]. Various breeds of cats have been documented including Domestic Shorthair, Himalayan, European, Persian, Siamese, and Domestic Longhair [205,208]. The underlying biochemical lesion is associated with a reduction in lipoprotein lipase activity. Subsequent biochemical studies indicate that the lipoprotein lipase (LPL) is produced in an inactive form similar to the class III type defect characterized in human LPL deficiency, and that heterozygous cats have intermediate LPL activity [210,211]. A mutation in the lipoprotein lipase gene is the molecular basis of chylomicronemia [212]. The condition is inherited as an autosomal recessive trait [205,208]. Pathologically, hyperchylomicronemia is characterized by presence of xanthomata (lipid granulomas) within many organs, including skin, liver, spleen, lymph nodes, kidney, adrenal glands, heart, and peripheral nerves [209]. These masses are distinguished by the presence of many large macrophages with vacuolated cytoplasm ("foam cells") within a coagulum of blood, degenerating blood components, fibrin, serum, and lipids. Ceroid, lipofuscin, hemosiderin, and crystal of triglycerides and cholesterol may also be seen. The xanthomata may be smooth, are often lobulated, and may be up to 5 cm in diameter. They are thought to arise either from frank hemorrhage or from the leakage of lipid-rich plasma perivascularly. Trauma is thought to predispose to xanthomata formation in peripheral nerves [205]. Nerve involvement is most noticeable at sites such as the spinal foramina and over bony prominences, where they are susceptible to stretching and compression associated with normal vertebral movement. Nerve bundles closely associated with the xanthomata show compression of fascicles (the masses typically are located outside the perineurium) which leads to secondary axonal degeneration and nerve fiber loss.

Clinical signs reflect involvement of various peripheral neuropathies:

- a. Horner's syndrome (ptosis, miosis, enophthalmos and prolapse of the third eyelid)
- b. Facial nerve paralysis (absence of corneal and palpebral reflexes)
- c. Tibial nerve paralysis (overflexion of the tarsus)
- d. Femoral nerve paralysis (atrophy of quadriceps muscles and absence of patellar reflex)
- e. Trigeminal nerve paralysis (temporal muscle atrophy, inability to prehend and chew food)
- f. Radial nerve paralysis (inability to extend digits)
- g. Recurrent laryngeal nerve paralysis (dyspnea and cyanosis due to impaired abduction of vocal cords).

Neuropathic signs are usually not seen until cats are at least eight months of age; however, paraplegia reportedly due to thrombotic occlusion of the aorta has been seen in an affected four week old Siamese kitten [208]. Recurrent pancreatitis and/or hepatosplenomegaly are rarely seen in affected cats [205].

Blood samples from affected cats have the appearance of "cream of tomato soup". Fundoscopic examination may reveal the presence of lipemia retinalis. Serum lipoprotein studies show a significant increase in chylomicrons and a smaller increase in very low density lipoproteins. Cholesterol and triglyceride serum values are increased and there is a significant reduction

in lipoprotein lipase activity. Other serum chemistry findings are within normal limits, including serum thyroxine levels. Prognosis is usually favorable, since all of the clinical manifestations of hyperchylomicronemia are reversible provided that the plasma triglyceride levels are reduced [205]. Peripheral neuropathies in affected cats resolve after 2 to 3 months on a low fat (e.g., as little as 10 g/day), high fiber diet. Gene replacement therapies are in progress [213]. A transient hyperlipidemia and anemia has been reported in kittens with significantly lower LPL activity (apo C-II function was normal) but without the above-mentioned LPL gene mutation [204]. None of these cats subsequently (as adults) developed xanthomata affecting nerve roots.

Idiopathic hyperlipoproteinemia is commonly seen in Miniature Schnauzers and Beagles with defective lipid metabolism characterized by hypertriglyceridemia and moderate cholesterol elevation [203]. The pathogenesis of this condition remains uncertain but may be associated with decreased activity of LPL. Abnormalities in lipoproteins include increased serum levels of low-density/very low-density lipoproteins with or without hyperchylomicronemia [201]. Affected animals have signs of abdominal distress, seizures, and occasionally, pancreatitis [214,215].

Secondary hyperlipidemia may occur in dogs and cats with various metabolic disorders including hypothyroidism, acute pancreatitis, diabetes mellitus, hyperadrenocorticism, and renal disease, and cholestatic hepatic disorders [201,216].

### **Hyperoxaluria**

Hyperoxaluria, primary or secondary, is occasionally seen in dogs and cats. Primary hyperoxaluria is considered to be an autosomal recessive disorder associated with renal failure from oxalate nephropathy and neurological signs in young Domestic Shorthair cats of either gender, resulting in death before one year of age [217-219]. This condition was initially observed in a closed cat colony in 1984. Affected cats develop acute renal failure between 5 and 9 months of age due to deposition of oxalate crystals within the kidney tubules. Signs include anorexia, dehydration, marked weakness, and depression. Kidneys are often enlarged and seem to be painful when palpated. Affected cats develop a crouching, cow-hocked stance, and are reluctant to stand or walk. Neurological examination reveals deficiencies in postural reaction testing, depressed patellar and withdrawal reflexes, absent cutaneous trunci reflex, and a reduced response to pain. Abnormal spontaneous potentials (positive sharp waves, fibrillation potentials, and high frequency discharges) are detected on EMG testing. Clinical signs in cats often deteriorate to the point that euthanasia is necessary. There is progressive increase in blood urea nitrogen and creatinine values, as well as increased serum levels of glucose, phosphate, and potassium. Urine contains increased oxalate and L-glycerate levels. Biochemical studies in affected cats have revealed deficient liver enzymatic activities of D-glycerate dehydrogenase and glyoxylate reductase, which are the deficient enzyme activities in human primary hyperoxaluria type 2 (PH2) [220]. Heterozygote cats appear to have intermediate liver levels of these enzymes.

Histopathological examination of kidneys reveal presence of numerous birefringent crystals within the tubules, interstitial fibrosis, and occasionally, periglomerular fibrosis. In the spinal cord, large swellings with a homogeneous appearance are observed in proximal axons of ventral horn cells. Ultrastructural examination shows that the swellings are due to accumulation of neurofilaments. Swollen axons are also seen in ventral roots, intramuscular nerves, and in dorsal root ganglia. Oxalate crystals are not observed within axons. Muscle changes are considered to represent neurogenic atrophy. Diagnosis may be made in affected cats before they develop clinical signs by identifying L-glycerate in urine. This metabolite is not present in urine of normal cats. Prognosis is grave. There is no treatment.

This inherited feline condition is now considered to be analogous to PH2 (L-glyceric aciduria) in people, an inherited condition characterized by recurring calcium oxalate kidney stones. The pathogenetic mechanisms associated with the lesions in the nervous system of the cats are not clear. Note that liver levels of the enzyme serine:pyruvate/alanine:glyoxylate aminotransferase, functional deficiency of which causes primary hyperoxaluria type 1 (PH1) in people and in Tibetan Spaniels [221,222], are normal in these cats. Peripheral nerve trunk involvement, as well as sensory and sympathetic ganglia, has been reported in people (but not in dogs) with PH1 with deposition of oxalate crystal within axons and in the walls of perineurial arterioles, leading to axonal degeneration, and demyelination [223,224]. Multiple calcium oxalate crystals are also seen in muscle surrounded by inflammatory infiltrates. In some patients with primary hyperoxaluria and renal failure, chronic hemodialysis may favor the development of neuropathy [225]. PH1 in people is an autosomal recessive disease. D-glycerate dehydrogenase/glyoxylate reductase levels are normal in people and affected dogs [222].

Secondary hyperoxaluria may also occur in cats and dogs following ingestion of the antifreeze ethylene glycol, which is metabolized to glycolic acid, glyoxalate, and oxalate. Oxalate nephrosis and renal sclerosis has been reported in a cat following renal transplantation [226]. There was no evidence of primary type 2 hyperoxaluria in this cat.

### **Hypertrophic Neuropathy**

Hypertrophic neuropathy is an autosomal recessive neurological disease that has been reported in Tibetan Mastiff dogs [227-230]. This disease is also known as canine inherited hypertrophic neuropathy. Clinical signs appear in animals from 7 to 10 weeks of age and consist of rapidly developing generalized weakness, hyporeflexia/areflexia, muscle hypotonia, and dysphonia. No other cranial nerve signs are reported. Severely affected puppies may become totally recumbent within 3 weeks of onset with subsequent development of sternal compression and limb contractures. Some puppies may regain the ability to stand and walk, but remain weak. Mild muscle wasting occurs and ambulatory puppies have a shuffling, plantigrade gait. Pain perception is normal.

Electrodiagnostic studies reveal progressive, moderate to severe reduction in nerve conduction velocities. Transient EMG abnormalities (positive sharp waves, fibrillation potentials, and high frequency potentials) may be seen early in the course of the disease but tend to disappear 2 or more months after onset of signs. Temporal dispersion of evoked muscle action potentials is reported in chronically affected dogs. There is variable elevation in CSF protein.

Pathologically, this disease results in a reduced density of myelinated fibers in peripheral nerves and nerve roots, widespread demyelination, and primitive onion-bulb formation with relatively little axonal degeneration. There is no inflammation. A constant feature is accumulation of actin-like filaments (6 to 7 nm in diameter) in Schwann cell cytoplasm, either in an adaxonal location or in cytoplasmic compartments within the myelin sheath. Experimental nerve transplantation studies point to a Schwann cell defect, possibly involving the cytoskeleton [231]. Ultrastructurally, some degenerating and remyelinating axons are surrounded by concentric layers of Schwann cell cytoplasm. Macrophages often invade the degenerating myelin sheaths. Morphological evidence of axonal injury is unusual, although ovoids and B  ngner's bands are occasionally seen.

Diagnosis is based on signalment, clinical, electrodiagnostic, and nerve biopsy data. Prognosis is guarded. There is no treatment. This canine hypertrophic demyelinating neuropathy has similarities to hereditary sensory and motor neuropathy (HSMN) type I, also known as Charcot-Marie-Tooth disease (CMT) type I, and HSMN type III (also known as Dejerine-Sottas disease, a variant of CMT) [43].

A condition that has some similarities to inherited hypertrophic neuropathy in the Tibetan Mastiff dog has been reported in two unrelated cats around 1 year of age with signs of intention tremor, mild sensory abnormalities, depressed reflexes, and urinary-fecal incontinence [232]. Grossly, peripheral nerves (motor/sensory and autonomic) appeared thickened.

Microscopic studies of peripheral and autonomic nerves revealed demyelination and onion-bulb formation, endoneurial fibrosis, and presence of inner perineurial mucoid masses. Axonal degeneration was not a feature. The condition was considered to resemble HSMN type I in people. Summers and colleagues also reported a hypertrophic neuropathy in a 1 year old male Domestic cat with generalized tremors, plantigrade gait, proprioceptive deficits, forelimb spasticity/hypermetria, progressive ataxia, and depressed nociception over paws, face and nasal vestibule [200]. Signs began around 7 months of age. Myelin sheaths of larger axons appeared thinly myelinated or demyelinated and there was onion-bulb formation. Ultrastructural changes revealed presence of filaments and accumulation of granular material within Schwann cell cytoplasm similar to that seen in Tibetan Mastiffs. Again, axonal changes were minimal. However, in their cat, degenerative changes (demyelination, spheroid formation, Wallerian degeneration, and astrocytic scarring) were observed in dorsal, lateral, and ventral funiculi of the spinal cord. Axonal degeneration extended to the medulla oblongata, caudal cerebellar peduncles, and accessory cuneate nucleus.

Pathological findings with some similarities to those seen in Tibetan Mastiffs have been observed in Beagle-Basset puppies (around 14 weeks of age), with widespread demyelinating radiculoneuropathy [200]. These puppies had megaesophagus, aspiration pneumonia, generalized weakness, diffuse muscle atrophy (especially proximally), absent patellar reflexes, and EDX findings of widespread denervation potentials (including facial and masticatory muscles) and decreased motor NCV.

### **Hypoglycemic Neuropathy**

Severe hypoglycemia (e.g., 18 to 45 mg/dl; normal = 80 - 120 mg/dL) in dogs and cats (less frequently) is most commonly associated with insulinomas with CNS signs of neuroglycopenia (generalized seizures, weakness, ataxia, collapse, lethargy, transient blindness, and abnormal behavior, e.g., hysteria) and sympathoadrenal stimulation (muscle tremors, nervousness, restlessness, and hunger) seemingly relating to the dependence of the CNS on glucose [103] (see hypoglycemia). An infrequently encountered complication of insulinoma-associated hypoglycemia in dogs is polyneuropathy [233-239]. Onset and clinical course may be acute to sub-acute (several days) or insidious/chronic (weeks to months). Clinical signs range from paraparesis to tetraplegia, facial paresis/paralysis, hyporeflexia/areflexia (e.g., myotatic and cutaneous trunci reflexes), hypotonia, and muscle atrophy (e.g., appendicular/masticatory/facial), sometimes in conjunction with seizures. In one report involving 3 severely-affected dogs, seizures or other signs of CNS dysfunction were not observed [238]. In another dog, seizures were seen approximately 16 months after initial signs of tetraparesis [239]. There is also a report of an affected dog with a history of recurring episodes of hind limb weakness, each episode lasting about 30 minutes, and with the dog appearing normal between episodes (seizures were not seen in this dog) [234]. Sensory nerve involvement is suggested by

presence of a lick granuloma in some dogs [233,234]. A subclinical polyneuropathy has also been reported in dogs [235]. Electrodiagnostic (EDX) testing has shown presence of abnormal spontaneous potentials (positive sharp waves, fibrillation potentials), and slowed motor nerve conduction velocities [235]. In several dogs, EDX data point to a distal distribution of the neuropathy (distal axonopathy), including presence of fibrillation potentials/positive sharp waves below the elbow and stifle [234,235]. CSF studies have been normal [239]. Histopathological findings in motor and sensory nerves from affected dogs include moderate to severe axonal necrosis, nerve fiber loss (affecting medium- and large-caliber myelinated fibers), and variable demyelination-remyelination [235,239,240]. Muscle changes reflect neurogenic atrophy, e.g., fiber size variation associated with scattered angular atrophic fibers and hypertrophic fibers (both type 1 and type 2A fibers, especially the latter). Diagnosis of insulinoma is based on the demonstration of high serum insulin level in the presence of fasting hypoglycemia (see hypoglycemia). The peripheral neuropathy diagnosis is suggested by clinical signs, and confirmed by EDX testing and nerve biopsy.

Treatment strategies have yet to be determined in dogs. Since most of the pancreatic tumors tend to be malignant (unlike the situation in people), prognosis is guarded to poor in dogs with insulinomas regardless of the presence of a polyneuropathy or not. In one report, oral treatment with prednisolone or prednisone at 1 mg/kg daily for 10 days and then every other day was successful in almost completely reversing all neurological signs for several months before the dog was euthanized because of occurrence of uncontrollable seizures [239]. Interestingly, there was no correlation between the blood glucose levels and clinical recovery (glucose levels remained low while insulin levels remained high when the dog was almost completely normal). Similarly, normalization of serum glucose levels using intravenous dextrose failed to improve clinical signs in one report involving 3 dogs with insulinoma-related neuropathies [238]. There is a report of clinical recovery in an ambulatory, hypoglycemic 7 year old female German Shepherd (with seizures, reduced exercise tolerance and dysphonia) following surgical removal of the insulinoma [241]. Streptozocin reportedly resulted in rapid reversal of the peripheral neuropathy in 2 dogs with pancreatic islet cell tumors [520]. The streptozocin was administered at a dosage of 500 mg/m<sup>2</sup>, IV, every 3 weeks and combined with a protocol for induction of diuresis.

In people, hypoglycemia-induced peripheral neuropathy due to insulinoma is uncommon, with only 34 patients being reported through 2000 [242]. The pathogenesis of the neuropathy remains unknown [110]. In people, the condition may be seen after several episodes of prolonged hypoglycemia, usually with obvious cerebral signs, and the neuropathy is typically symmetrical, predominantly distal, and usually sensorimotor [242]. A less severe polyneuropathy (predominantly sensory) occurred in schizophrenic patients treated with insulin shock therapy [243]. Experimental studies suggest that severe and mild hypoglycemia causes a distal axonopathy, with motor axons appearing more vulnerable than sensory axons [242,244-247]. Further, experimental studies indicate that nerve damage may result from the hypoglycemia due to disruption of fast anterograde axonal transport [248]. Both duration and severity of hypoglycemia (e.g., blood glucose < 1.5 mmol/L or 27 mg/dL and > 12 hours) appear to be risk factors for axonal degeneration [249] which, in one experimental study, occurred mainly in central fascicular regions of distal peripheral nerves, suggesting deficiency of energy substrate due to poor perfusion in watershed zones [250]. Impaired motor nerve conduction velocities and axonal atrophy have also been reported [251]. There is also the possibility that the hypoglycemia-induced peripheral neuropathy due to insulinoma represents a paraneoplastic neuropathy [236,239,247,252]. Paraneoplastic syndromes in humans are thought to be immunologically mediated since some patients have circulating antibodies that recognize antigens shared by neural elements and tumor cells [253]. The remarkable clinical response to corticosteroids in the canine case reported by van Ham and associates [239] certainly suggests possible immune-mediated pathogenetic mechanisms. Although a sensorimotor, symmetric, and predominantly distal neuropathy may be seen in human patients with paraneoplastic neuropathies (including insulinomas), no tumor-related immunologic alteration has yet been identified similar to the circulating antineuronal antibodies found in patients with paraneoplastic subacute sensory neuropathy (usually occurring in association with small cell lung cancer) [254]. In people, other possible causes of the neuropathy have included toxic factors produced by the tumor, metabolic causes (e.g., the tumor competing with the host for essential metabolites), vitamin/nutritional deficiency, vascular causes (e.g., vasculitis), and viral infections causes; however, definitive proof is lacking for each of these [252,255].

### **Hypothyroid Neuropathy**

Hypothyroidism is common in dogs but rare in cats and most cases of acquired canine hypothyroidism are associated with immune-mediated lymphocytic thyroiditis/idiopathic thyroid atrophy [256,257]. A hypothyroid-associated neuropathy commonly occurs in mature to middle-aged dogs, usually of the large-breed variety. The few cases reported in the literature [258-261] do not reflect the prevalence of this metabolic neuropathy, based on muscle and nerve biopsy material that we have examined (both at the Scott-Ritchey neuromuscular laboratory at Auburn University and at my peripheral nerve laboratory) from numerous hypothyroid dogs. Sub-clinical cases have been recognized [534]. Clinical signs may include exercise intolerance, progressive weakness (e.g., paraparesis, tetraparesis), muscle atrophy (mainly appendicular) and depressed spinal reflexes. Other signs may include pelvic limb proprioceptive deficits, unilateral/bilateral facial nerve paresis/paralysis, ventrolateral strabismus, and decreased corneal/facial sensitivity. Intermittent forelimb lameness is less

commonly reported [533]. In one comprehensive study of the neurological manifestations of hypothyroidism in 29 dogs, lower motor neuron signs were seen in 11 dogs, 9 dogs had peripheral vestibular deficits, 4 had megaesophagus, and 5 had laryngeal paralysis [260]. Peripheral neuropathy has been seen in several hypothyroid dogs with megaesophagus and myasthenia gravis [261]. Electrodiagnostic studies in appendicular muscles have revealed multifocal patterns of fibrillation potentials, positive sharp waves, decreased motor and sensory nerve conduction velocities, and complex repetitive discharges. Similar changes may be found in facial muscles. In some instances, there is a lack of correlation between the degree of EMG abnormalities and the severity of the clinical weakness [258]. Dogs with vestibular deficits may have abnormal brainstem auditory-evoked responses [260]. CSF analysis usually reveals normal cellularity with normal or mild/moderate protein increase (25 - 110 mg/dL) [259,260]. Serum cholesterol levels are usually increased. Muscle changes reflect varying degrees of neurogenic atrophy (angular atrophy of muscle fibers, especially type 2 fibers; compensatory hypertrophy) while teased nerve fiber studies and semithin sections are typically characterized by mixed pathology involving demyelination/remyelination and axonal necrosis. The underlying pathology appears to be a sensorimotor polyneuropathy and, based on my experiences, at least some of these cases have a distal distribution (i.e., distal sensorimotor polyneuropathy).

Diagnosis is based on serological evidence of hypothyroidism (low serum T4 concentration and inadequate response to thyroid-stimulating hormone administration) [260]. Prognosis is often favorable. In one study involving 29 dogs, most dogs recovered within 2 to 3 months of thyroid hormone supplementation (20 µg/kg of L-thyroxine PO bid). Dogs with megaesophagus improved over 4 months, while dogs with laryngeal paralysis showed partial improvement after 5 months. One caveat is that we have encountered a number of dogs in which there is less dramatic or no clinical response to long-term thyroid hormone supplementation.

Note that affected dogs may also have generalized signs of hypothyroidism, including thinning of the haircoat, alopecia, dry skin with epidermal scales and flaking, etc.

The pathophysiology surrounding hypothyroid neuropathy remains unexplained [262]. In people with hypothyroidism, a mild peripheral neuropathy is relatively common and may include facial mononeuropathy, sensorineural hearing loss, distal sensory neuropathy, and sensorimotor polyneuropathy [103,263]. One study reported changes in nerves consistent with a dying back process and possible underlying slow axonal transport [264]. There may be preferential loss of larger caliber myelinated fibers [265]. Carpal tunnel syndrome (median nerve mononeuropathy at the wrist) is the most common mononeuropathy encountered [103]. As we have seen in dogs, the relative proportions of axonal degeneration (secondary to disturbance of neuronal metabolism?) and demyelination (primary Schwann cell involvement?) varies from case to case [264,266,267]. Onion bulb formations are infrequently found. Ultrastructural changes in affected human nerves include prominent cluster formations and excessive glycogen deposition in Schwann cells, myelinated and unmyelinated axons, endothelial cells, and perineurial cells [265,268].

### **Laryngeal Paralysis**

Innervation of three of the four intrinsic laryngeal muscles (dorsal and lateral cricoarytenoid muscles and thyroarytenoid muscle) comes from the special visceral efferent axons of the recurrent laryngeal nerves. The fourth muscle (cricothyroid muscle) is supplied by the motor branch of the cranial laryngeal nerve [269]. The recurrent laryngeal nerve on each side is derived from the vagus nerve which in turn originates from the nucleus ambiguus in the brainstem [149]; so theoretically, a lesion in any of these anatomic locations might lead to laryngeal dysfunction. The efferent axons to the larynx are categorized as special visceral efferent fibers [149]. Laryngeal paralysis (LP) classically results from unilateral or more commonly, bilateral denervation of the laryngeal abductor muscles (dorsal cricoarytenoid muscles), which leads to impaired abduction of the vocal fold(s), glottic obstruction, and dyspnea [269-271].

Hereditary, idiopathic, and acquired forms of this potentially fatal disorder have been reported in dogs and cats. A hereditary form (autosomal dominant) has been documented in Bouvier des Flandres dogs either as unilateral or bilateral disease [270,272,273]. A inherited or presumed hereditary form has been reported in young Siberian Huskies, Husky cross-breeds, Bull Terriers, Dalmatians, Rottweilers, white-coated German Shepherds, and Pyrenean Mountain dogs [172,271,274-277,531]. Affected Huskies share a phenotype of blue eyes, and white freckled face. LP has also been recently reported in young Rottweiler puppies in association with neuroaxonal dystrophy [278] and spongy degeneration of the CNS [279]. The idiopathic form has been reported mostly in middle-aged and older large and giant breed dogs, such as St. Bernard, Chesapeake Bay Retriever, Irish Setter, Afghan Hound, Labrador Retriever and Rottweiler, but medium and small/toy breeds also may be affected [269,280-282]. Male dogs, particularly if castrated, were more frequently affected than females in one reported survey [280]. In another study, the severity of the laryngeal paralysis was correlated with increasing age in larger breed dogs [283]. Acquired LP is sporadically reported in dogs. Bilateral LP resulted from entrapment of both recurrent laryngeal nerves by fibrous tissue surrounding a peritracheal abscess (thought to be caused by a foreign body penetrating the wall of the esophagus) in an 8 month old Cocker Spaniel [284]. LP has also been seen in dogs as a surgical complication in the treatment of carotid body tumors [285] and thyroid carcinomas [286]. Trypanosomiasis was considered



to be the cause of LP in a 12 year old Labrador Retriever [287]. Laryngeal paralysis may be one of several signs seen in animals with rabies. LP in some older dogs has also been linked with hypothyroidism (see hypothyroid neuropathy) [260,280,281,288,532]. LP has also been reported in two older dogs as a possible complication of paraneoplastic neuropathy (both dogs were also hypothyroid) [289]. Dysphonia/LP may also be observed in animals with coonhound paralysis/idiopathic polyradiculoneuritis, chronic inflammatory demyelinating polyneuropathy, in German Shepherd dogs with giant axonal neuropathy, and in some dogs with sensory ganglioradiculitis.

In cats, congenital and idiopathic forms of LP have been reported sporadically and earlier reports favored castrated males [290-292]; however in a more recent study, no gender or breed predilection was noted, although 7/8 male cats were neutered and all females were spayed [293]. Acquired LP in cats has been reported as a result of trauma to the neck [294], lymphomatous infiltration of the vagus nerve [295], cystic thyroid adenoma [296], adenocarcinoma of the tympanic bulla and damage to the recurrent laryngeal nerve [297], and seen as a complication of lead poisoning [298], percutaneous ethanol injection for the treatment of hyperthyroidism [299], surgical repair of intrathoracic tracheal avulsion [300], surgical thyroidectomy [301], and other neck/mediastinal surgeries (e.g., removing a thyroid adenoma, ligation of a patent ductus arteriosus, thymectomy) [302,303].

Onset of clinical signs in the congenital/hereditary forms of LP in dogs is from 4 to 6 months of age. The acquired and idiopathic forms usually develop in older animals from 1 to 13 years of age. Clinical signs reflect respiratory, primarily inspiratory, distress and are characterized by increasing loss of endurance, progressive laryngeal stridor (especially on exertion), voice changes (dysphonia), dyspnea, cyanosis during episodes of severe dyspnea, and collapse with complete airway obstruction. Clinical signs are usually of several months duration. In cats, excessive head shaking and abnormal purring may also be noted. Megaesophagus is usually not a clinical feature of LP in cats, although it has been confirmed radiographically in occasional cats [293]. Note that unilateral paralysis (also termed laryngeal hemiplegia) in dogs may be subclinical [269,270], although in working dogs, such as racing Greyhounds and Siberian Husky sled dogs, unilateral paralysis can result in obstructive dyspnea and interfere with racing function [269]. In cats, unilateral LP can be subclinical [294] or result in mild clinical signs. Unilateral congenital and idiopathic forms tends to affect the left side of the larynx in dogs and cats [270,293].

Diagnosis of LP is based on clinical signs, laryngoscopy showing impaired abductor dysfunction, and EMG evidence of denervation potentials in the intrinsic laryngeal muscles. Ultrasound (echolaryngography) may also be a useful diagnostic technique [304]. There is histological evidence of neurogenic atrophy in laryngeal muscles. In the Bouviers, lesions found in the recurrent laryngeal nerves (e.g., axon fragmentation, digestion chambers, endoneurial fibrosis) were found at all levels of the nerves and were considered to be secondary to lesions involving the nucleus ambiguus [270]. Gliosis and neuronal atrophy of the vagal nuclei were reported in an affected Husky Cross puppy [271]. Degenerative changes, including axon and myelin degeneration, axonal loss, and endoneurial fibrosis have been noted in recurrent laryngeal nerve samples from older dogs with idiopathic LP [269].

Laryngeal paralysis has also been noted in dogs with clinical, electrodiagnostic (EDX), and pathological evidence of a more generalized polyneuropathy [281], which has been termed laryngeal paralysis polyneuropathy complex (LPPC) [172]. This condition has now been seen in young Dalmatians, Rottweilers, and Pyrenean Mountain dogs [172,276,277]. In addition to the clinical signs described above, other neurological abnormalities associated with the laryngeal paralysis included spinal hyporeflexia, limb muscle atrophy or fasciculations, limb hyperextension, facial/lingual paralysis, and hypermetria.

Megaesophagus was a common feature in affected Dalmatians and Pyrenean Mountain dogs (megaesophagus was found in one affected Rottweiler, while regurgitation was associated with hiatal hernia/gastroesophageal intussusception in another puppy). Four of the five Rottweiler puppies had bilateral lenticular cataracts. Bilateral paralysis of the vocal folds (arytenoid cartilages) was noted in all dogs (although not always symmetrical) under light sedation. EMG abnormalities included fibrillation potentials and positive sharp waves in a variety of muscles including laryngeal, esophageal, facial, masticatory, and distal appendicular muscles. Nerve conduction velocities (NCVs) may be normal or mildly decreased. Direct evoked compound muscle action potentials have shown low amplitude without evidence of dispersion (polyphasic waves), suggestive of axonal degeneration. Congenital deafness has been demonstrated in several dogs using BAER testing.

Neurogenic atrophy was observed in intrinsic laryngeal and appendicular muscles. Changes in cranial and appendicular nerves (motor and sensory, as well as in autonomic nerves) were dominated by axonal necrosis and loss of medium sized and larger-caliber myelinated fibers, with the intensity of the changes being more severe in distal parts of nerves (e.g., recurrent laryngeal nerve). Ultrastructural changes included loss of myelinated fibers, variable ovoid presence, marked increase in endoneurial collagen, numerous Büngner bands (denervated Schwann cells), and evidence of unmyelinated fiber involvement (e.g., collagen pockets, flattened axons, empty Schwann cell subunits). To date, no lesions have been found in the nucleus ambiguus of the brain stem. Morphological, morphometric, and/or EXD studies suggest that LP in Dalmatians, Rottweilers, and Pyrenean Mountain dogs represents a distal axonopathy (or dying-back disease).

While O'Brien and colleagues stated that no clinical evidence of central or peripheral nerve deficits were found in their cases of idiopathic LP in older, larger breed dogs (although they reported Wallerian degeneration in sciatic nerve from one

affected dog) [269], paresis and foot drop due to denervation of the cranial tibial muscle have been occasionally observed in affected young Bouviers [270]. Furthermore, signs of pelvic limb weakness are sometimes seen in older dogs with idiopathic LP [280,281]. In these animals, pelvic limb reflexes may be diminished and there may be evidence of abnormal spontaneous potentials (fibrillation potentials and positive sharp waves) on EMG studies, along with slowed motor NCVs. Muscle/nerve biopsies may show neurogenic muscle atrophy, (e.g., scattered angular atrophic fibers, small fiber group atrophy), demyelination, and variable axonal degeneration [281]. A more generalized neurological disorder has also been observed in two cats with laryngeal paralysis that were eventually euthanized because of progressive neuromuscular signs [292]. In summary, it appears that hereditary and idiopathic forms of LP in dogs and cats often may be related to a more generalized polyneuropathy.

Serum cholinesterase activity, thyroid testing, serum antinuclear antibody and rheumatoid factor titers, Coombs testing, and serum anti-acetylcholine receptor antibody levels are normal in dogs with LPPC, and there is no evidence of lead toxicity. Prognosis in dogs with congenital/hereditary LP is guarded to poor, especially if megaesophagus is present due to the high risk of inhalation pneumonia. Feeding of a liquid gruel from an elevated platform may be beneficial in dogs with megaesophagus. Laryngeal tie-back surgical procedures may provide dramatic relief of the dyspnea, but multiple surgeries may be required during the first 12 months. Additional complications in dogs are joint contractures (especially the carpus), which may be surgically managed by arthrodesis. Conversely, idiopathic paralysis in older dogs may have a favorable prognosis since megaesophagus is typically not a feature of the disorder, clinical signs of more generalized peripheral nerve disease appear to milder, and the dominant pathology in nerves is more likely to be demyelination rather than axonal degeneration. Harvey and colleagues reported that thyroid hormone supplementation resulted in marked clinical improvement in their older hypothyroid dogs with LP [288]. Surgical management, such as arytenoidectomy and vocal fold removal, arytenoid lateralization, cricoarytenoid laryngoplasty, and castellated laryngofissure may be very effective [292,305-308]. In one experimental study, bilateral arytenoid cartilage lateralization produced more consistent clinical improvement, a wider rima glottidis, increased inspiratory air flow, and a significant increase in post-operative arterial oxygen tension when compared to castellated laryngofissure [309]. Thyroarytenoid lateralization also requires less surgical time to perform than cricoarytenoid laryngoplasty [307]. Despite favorable reports, it should be noted that surgical repair of idiopathic/acquired forms of laryngeal paralysis may be associated with high postoperative complications (particularly aspiration pneumonia) and mortality rates [532]. (These complications were more commonly associated with bilateral arytenoid lateralization and partial laryngectomy techniques). Surgical intervention is also beneficial in cats with idiopathic LP [293,302], although prognosis is guarded to poor in suspected congenital/idiopathic cases developing progressive neuromuscular disease [292]. Prognosis for cats with mild signs (e.g., in those with traumatically-induced unilateral LP) may be favorable with conservative treatment, such as moving cats indoors, avoiding excitement, and restricting exercise [293]. Prognosis for animals with acquired LP will usually depend on the underlying cause. In cats with subclinical traumatic laryngeal hemiplegia, resolution of the impaired arytenoid cartilage abduction occurred spontaneously over several months [294]. Prevention of the inherited form by breeding control is indicated.

Note that LP may also be a component of the hereditary Alaskan Malamute polyneuropathy that was thought to be eradicated in Norway in 1982 [6]. Dysphonia has been observed in some Alaskan Malamutes with a similar if not identical condition that has been reported recently in the United States and Germany [3,4].

### **Optic Neuritis**

Optic neuritis is an inflammatory condition of the optic nerve(s) that results in loss of vision. It may be associated with primary ocular disease or can occur secondary to systemic inflammatory disease. In most animals, the underlying cause is not determined. The condition is not uncommon, affecting dogs [310,311] more frequently than cats [312,313]. There is no apparent breed or gender predisposition, however, most affected dogs are older than 3 years of age.

In dogs, diagnostic considerations include canine distemper, ocular form of granulomatous meningoencephalomyelitis, systemic mycosis (e.g., cryptococcosis, blastomycosis), toxoplasmosis, neoplasia, trauma, and acute toxicity (e.g., lead, chlorinated hydrocarbon, or clioquinol toxicity, and closantel intoxication) [78,314-327]. Optic neuritis may also be seen as a complication of uveodermatologic syndrome, a disorder characterized by bilateral panuveitis and skin and hair depigmentation that is similar to human Vogt-Koyanagi-Harada syndrome in people [328], although the associated meningitis in the human disease has not been reported in dogs.

An apparently healthy animal may present with a history of unilateral or bilateral blindness of sudden onset. Pupils usually are unilaterally or bilaterally dilated and unresponsive to light stimulation. The disorder may be associated with orbital pain or pain with ocular movement [329]. Ophthalmoscopic examination may or may not be helpful. Ophthalmoscopic abnormalities may include an edematous, elevated optic disk and engorged retinal vessels. Focal hemorrhage may be present. Active or inactive chorioretinitis may accompany the optic neuritis. Atrophy of the optic nerve frequently follows repeated episodes of acute optic neuritis. Optic neuritis is distinguished from papilledema in that vision is preserved in the latter condition. Optic neuritis is termed "intraocular" if fundic changes are seen ophthalmoscopically or "retrobulbar" if no

changes are seen (note that acute optic neuritis is often retrobulbar) [329]. Neurological exam is frequently normal. The first line of treatment should be directed at the primary disease process that initiated the optic neuritis. However, since the cause is frequently undetermined, the animal may be treated symptomatically with retrobulbar corticosteroids (e.g., betamethasone, 2.5 mg) in conjunction with oral corticosteroid administration (e.g., prednisolone, at 2 mg/kg daily, divided bid, for 10 to 14 days, followed by half this dosage for two more weeks, and gradual reduction to maintenance therapy every other day for up to one year). Prognosis is guarded. Clinical response to treatment can be difficult to assess and the course is unpredictable. Some animals have a return of vision within 1 or 2 days, while others may show only gradual improvement over several months. Clinical exacerbations may occur if treatment is prematurely stopped. In some animals, the disease process may progress, resulting in permanent structural changes and irreversible blindness. Optic nerves were involved in a subclinical, inflammatory demyelinating CNS disorder in cats characterized by infiltrating lymphocytes, plasma cells and macrophages, and intracytoplasmic inclusions consisting of tubular structures with similarities to paramyxovirus nucleocapsids [330,331].

### **Paraneoplastic Neuropathy**

The frequency of peripheral neuropathy in human patients with cancer (see also paraneoplastic disorders) varies with the screening technique employed. The clinical incidence of some forms of paraneoplastic neuropathy has been estimated to be 5 to 16% [254]. This figure increases to more than 40% if quantitative sensory testing or electrophysiological / pathological evaluation are performed, reflecting the high incidence of subclinical neuropathy [252,332-334]. As stated by Mcleod [255], the actual frequency of peripheral neuropathy in malignancy is difficult to ascertain since it "...depends on the pathological type and site of tumor, the stage and duration of the illness, the diligence with which it is sought, the techniques of investigation employed, and the criteria for diagnosis". Several paraneoplastic neuropathies have been recognized in human cancer patients [252,254,255,332]: subacute sensory neuropathy, sensorimotor neuropathy (including mild terminal neuropathy, severe rapidly evolving or relapsing sensorimotor neuropathies, microvasculitic neuropathy, and sensorimotor neuropathies associated with malignant monoclonal gammopathies), Guillain-Barré syndrome that is sometimes seen in association with Hodgkin's disease, and brachial plexitis. Paraneoplastic autonomic dysfunction may occur, usually accompanying other paraneoplastic syndromes. Pathological findings vary with the particular paraneoplastic neuropathy [254,255]. In subacute sensory neuropathy (SSN), there is loss of neurons in spinal ganglia along with focal inflammatory infiltrates, and dorsal column degeneration. In paraneoplastic sensorimotor neuropathies, axonal or demyelinating changes, either inflammatory or non-inflammatory, may be observed. The pathogenesis of some forms of paraneoplastic neuropathies appears to be related to molecular mimicry in which antibodies produced against the tumor cross-react with neural antigens, e.g., SSN is associated with circulating (serum and CSF) antineuronal antibodies (anti-Hu) expressing specificity for neuronal nuclear antigens [335,336]. In most instances, the malignancy is small cell lung cancer. In contrast to SSN, the underlying pathogenesis of paraneoplastic sensorimotor neuropathies (much more common than SSN) remains unclear but appears unassociated with immunological mimicry (no tumor-specific antibodies have been recognized) or tumor toxin [255]. The malignancy often involves the lung, but carcinomas have been found in a variety of organs (e.g., pancreas, stomach, rectum, uterus, breast, colon, cervix, kidney, prostate, and testis) [255]. Some forms of paraneoplastic sensorimotor neuropathies may represent dying-back axonopathies [254]. In some instances, paraneoplastic neuropathies may be obscured by neurotoxic chemotherapeutic agents, metabolic disorders, and inactivity [252].

The clinical or subclinical incidence of PNS paraneoplasia in animals is presently unknown; however, peripheral nerve lesions may be facilitated by presence of certain types of cancer in animals, as in people. In one prospective qualitative and quantitative study on the effects of cancer on the PNS in dogs, the highest percentage of abnormalities in teased nerve fibers from dogs with malignancies were found in bronchogenic carcinoma (59%), mammary adenocarcinoma (59%), malignant melanoma (48%), insulinoma (47%), osteosarcoma (39%), thyroid adenocarcinoma (35.5%) and mast cell tumor (32%) [236]. The major histopathological findings in this study included paranodal-segmental demyelination, remyelination, axonal degeneration, and myelin globules. Overall, 16 of 21 dogs (76%) had a significantly greater number of lesions in peripheral nerves than age-matched controls. It is interesting to note that two of the tumor cases in our prospective study (those with the highest number of abnormalities) were bronchogenic carcinomas. Such tumors have long been recognized for their intimate association with paraneoplastic neuropathies in people [337,338]. It was also evident that different types of malignancies (mammary adenocarcinoma, malignant melanoma, insulinoma, osteosarcoma, etc.) resulted in a differing incidence of neuropathy, a finding also well-recognized in human cancer patients. In addition, the severity of the neuropathy sometimes varied markedly with tumors of the same type, probably reflecting differences in the stage and duration of the illness. Of all the malignant tumors in our study, lymphosarcoma appeared to have the least neuropathic effect. The neuropathies in dogs of this study were mainly subclinical.

Clinical hallmarks of the neuropathic syndrome are reduced or absent spinal/cranial reflexes, flaccid weakness, reduced muscle tone, paralysis of limb or head muscles, and after 1 to 2 weeks, neurogenic muscle atrophy. Dysphonia may also be detected. Clinical neuropathies have been seen sporadically in dogs with malignant tumors, including bronchogenic

carcinoma, insulinoma, lymphosarcoma, fibrosarcoma, leiomyosarcoma, hemangiosarcoma, and undifferentiated sarcoma [170,234,235,289,339-341]. In two of these reports, the neuropathies had a distal distribution based on electrodiagnostic (EDX) and pathological studies [235,289]. Abnormal EDX findings include fibrillation potentials, positive sharp waves, and slowed motor nerve conduction velocities. In my peripheral nerve laboratory, I have examined nerve samples from dogs with synovial cell sarcoma and adrenal adenocarcinoma that were accompanied by clinical neuropathies.

In contrast with people [342], malignant monoclonal gammopathies (dysproteinemic neuropathies) rarely seem to involve the peripheral nerves in dogs or cats [343,344]; however, a polyneuropathy (based on EMG findings) was reported in a 12 year old German Shepherd with multiple myeloma and monoclonal hypergammaglobulinemia [345]. In people, dysproteinemic neuropathy or NAP (neuropathy associated with paraproteinemia) are relatively common and the paraproteins (circulating immunoglobulins, or M-Proteins) may be IgM, IgG, or IgA, consisting of the whole immunoglobulin molecule or only the heavy or light chain [342]. Diseases associated with NAP include monoclonal gammopathies of unknown significance (MGUS), multiple myeloma, Waldenström's macroglobulinemia, osteosclerotic myeloma/POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes), primary amyloidosis, lymphoproliferative diseases (lymphoma, leukemia), heavy chain disease, and cryoglobulinemia [342,346]. The majority of NAP cases appear to be IgM with myelin sheath anti-MAG (myelin-associated glycoprotein) activity and characteristic widely-spaced myelin lamellae (associated with separation of the intraperiod line), along with evidence of a distal sensorimotor symmetrical neuropathy characterized by demyelinating changes (active myelin breakdown, denuded axons, thinly myelinated fibers, and onion-bulb formations) [342,347]. Axonal degeneration and loss of myelinated fibers may also be present, especially in chronic cases.

Too few cases have been documented to evaluate treatment strategies of paraneoplastic neuropathies in dogs and cats. In a recent report, antineuronal antibodies were not found in 120 dogs with extraneural tumors suggesting that screening for ANNA may not be useful for detecting dogs with paraneoplastic neuropathies [516]. Prognosis is guarded to poor in cases that have been reported, although recovery occurred in one dog following surgical removal [341] and in another with multiple myeloma treated with melphalan and prednisolone [345].

### **Peripheral Nerve Tumors**

Readers are referred to chapter 2 and Neoplasia of the Nervous System for a review of neoplasms involving peripheral nerves (see peripheral nerve tumors).

### **Polyradiculoneuritis**

By definition, polyradiculoneuritis is an inflammatory condition primarily involving multiple nerve roots. It may be one of the more commonly observed and least understood conditions in dogs and cats. It is becoming evident that there are a number of nerve root disorders (polyradiculoneuritides or polyradiculoneuropathies) that are characterized clinically by sudden onset of paresis, paralysis, or tetraplegia. Cranial nerve involvement may be prominent and there may be a relapsing clinical course. Differentiation of these conditions from pure primary peripheral nerve disorders (those without nerve root involvement) or junctionopathies can be difficult but may be facilitated by electrodiagnostic (EDX) testing [86,348]. With nerve root lesions, there may be abnormal latencies in F-waves (small compound muscle action potentials [CMAPs] resulting from antidromic excitation of motor neurons) or H-waves (small CMAPs that occur following nerve stimulation resulting from impulses in sensory nerve fibers that monosynaptically excite ventral horn cells). The latency of the H-wave is about the same as the F-wave but requires functional dorsal roots, in addition to ventral roots and proximal peripheral nerve). Additional EDX testing includes determination of compound action potential amplitudes, F-ratios, F-wave amplitudes, and electromyography [349]. There may be increased levels of CSF protein without pleocytosis (albuminocytologic dissociation), and nerve root biopsy may show evidence of inflammatory cell infiltration. It is likely that many cases of polyneuritis are actually polyradiculoneuritides. A tentative classification of polyradiculoneuritis in dogs and cats follows. Readers should note that Coonhound paralysis and Idiopathic polyradiculoneuritis described below have been termed "acute canine polyradiculoneuritis" by some authors [433].

### **Coonhound Paralysis -**

Coonhound paralysis (CHP) is a sporadically-occurring neurological disease of dogs, occurring especially in raccoon-hunting breeds [350-353]. The pathogenesis is unknown. A raccoon bite has been a consistent antecedent in CHP. The condition has been reproduced experimentally by injection of raccoon saliva into a dog that had recovered from two earlier spontaneous attacks [354]. Results of this work suggested that raccoon saliva contains the etiologic factor for CHP and that only specifically susceptible dogs are at risk of developing CHP when exposed to this factor.

Interest has focused on CHP due to its resemblance to Guillain-Barre syndrome (GBS) in people and its potential as an elucidating model. Like the human syndrome, CHP may have an immunological pathogenesis, although results of one study of CHP did not conform with the evidence presented in GBS for an obligatory role of macrophages in initiating myelin

damage [355]. However, the observed changes do resemble those reported in immunological-mediated experimental allergic neuritis [356].

Pathological findings are associated with a polyradiculoneuritis, with both segmental demyelination and concurrent degeneration of myelin and axons. Leukocytic infiltration, consisting mostly of cells of the monocyte-macrophage series, and scattered aggregates of lymphocytes and plasma cells also are observed. Changes occur in peripheral nerves and nerve roots, especially in the latter and more consistently in ventral roots than dorsal roots. In one comprehensive study, lumbosacral roots and spinal nerves were more involved than thoracic and cervical roots and spinal nerves [357].

Neutrophils may be present early in severely affected dogs. Chromatolytic changes in spinal motoneurons may occur secondary to severe axonal degeneration in peripheral nerves and nerve roots.

The disease affects dogs of any breed, both sexes, and usually of adult age. Clinical signs frequently appear 7 to 11 days after an encounter with a raccoon. Onset is marked by weakness and pelvic limb hyporeflexia, although thoracic limb involvement may sometimes be the initial and dominant clinical sign. Paralysis progresses rapidly, resulting in a flaccid symmetric tetraplegia; however, milder forms without paralysis can occur. The duration of paralysis varies from several weeks to 2 or 3 months. Motor impairment is more pronounced than sensory changes, although many dogs appear to be hyperesthetic to sensory stimuli. Bladder and rectal paralysis are not usually observed. In severely affected animals, there may be complete absence of spinal reflexes, facial weakness, loss of voice, inability to lift the head, and labored respiration. Motor nerve conduction velocities may be markedly reduced and EMG studies reveal widespread denervation 6 to 7 days after the onset [355]. F-waves can be altered (e.g., prolonged F-wave latencies and F-wave dispersion, decreased F-wave amplitudes), depending on the clinical signs and duration of disease [358]. In addition, increased F-ratios, and decreased CMAPs may be helpful EDX features [349]. Note that in some cases, the EDX changes appear to have a distal distribution. Similar findings occur in people with GBS and it has been explained by the preferential involvement of longer nerves associated with their greater chance of being affected by a multifocal demyelinating process [524]. Elevated protein with normal cell counts in CSF has been reported, especially in samples obtained from lumbar puncture [353]. This protein is predominantly albumin and its origin is thought to be more consistent with protein transudation rather than intrathecal immunoglobulin production [511]. Presence of circulating antibodies against raccoon saliva has been demonstrated using ELISA assays [358].

Prognosis is usually favorable, but dogs with severe axonal degeneration may die from respiratory paralysis or may have protracted, incomplete recoveries, and some animals may not show any clinical improvement. Protection from future attacks is short-lived or nonexistent. Affected dogs may have a greater chance of redeveloping paralysis on subsequent encounters with raccoons [353]. Treatment is symptomatic. Corticosteroids in our experience have not been effective in expediting recovery. Good nursing care is essential, including physiotherapeutic rehabilitation.

In people, GBS (or acute inflammatory demyelinating polyradiculoneuropathy) appears to be an autoimmune disease, involving both cell-mediated and humoral factors (e.g., IgG and IgM antibodies) resulting from aberrant immune responses against various components of peripheral nerve fibers (the myelin sheath is the specific target structure) and is characterized by presence of inflammatory lesions (lymphocytes and macrophages) and localized demyelination throughout the PNS [347]. Axonal lesions also occur but are usually less severe than the demyelinating lesions. However, two forms of axonal-GBS are recognized: acute motor-sensory axonal neuropathy and acute motor axonal neuropathy [359,360]. Some forms of GBS appear to be related to *Campylobacter jejuni* infection (especially the axonal forms), while other antecedent events (or "triggers") include viral and spirochete infection, surgery, and vaccination (including some strains of rabies) [347]. While the existence of a primary axonal neuropathy in a small percentage of human patients having a poor prognosis has been reported [361,362], we found that the intensity and type of lesion in 13 GBS patients with severe clinical disease (all bedridden in an intensive care unit and most requiring assisted ventilation) had no predictive value for eventual clinical recovery, but was correlated with length of clinical course (axonal lesions dominated in 23% of patients, while axonal lesions in presence of the more classical demyelinating form of GBS was seen in a further 23% of patients) [363]. In people, supportive care is the cornerstone of treatment as the majority of patients recover once the acute stage is passed, while specific treatment includes plasmapheresis and intravenous immunoglobulins [347]. Corticosteroids are usually ineffective.

### **Idiopathic Polyradiculoneuritis -**

A condition that appears to be identical to Coonhound paralysis with respect to onset, clinical signs, clinical course, EDX findings, and pathology occurs in dogs that have had no possible exposure to raccoons [364,365]. This condition has a world-wide distribution, occurs in countries where raccoon do not exist [366] and may have an incidence much higher than the literature suggests [367-369]. Mature dogs are typically affected; however, a suspected polyradiculoneuritis has also been reported in a 14 week old Rottweiler puppy in the UK [370]. Note that mild forms of polyradiculoneuritis may occur in dogs in which flaccid paralysis does not develop fully in any muscle group and animals maintain ambulatory function [368]. As with Coonhound paralysis, some dogs with idiopathic polyradiculoneuritis may require ventilatory support [367]. In my experience, pathological findings in peripheral nerve biopsy samples (e.g., common peroneal nerve) reflect the clinical

course of idiopathic polyradiculoneuritis: minimal changes are seen within the first 7 to 10 days of clinical signs. In chronic cases, the incidence of changes increases, usually reflecting a mixture of axonal degeneration, demyelination, and remyelination. Idiopathic polyradiculoneuritis is clinically, but not pathologically, similar to distal denervating disease, reportedly the most common canine polyneuropathy in the UK. In a recent study examining the relationship between acute polyradiculoneuritis and prior infection or exposure to various infectious agents, affected dogs had significantly higher serum IgG titers against *Toxoplasma gondii* than controls, although a causal relationship was not established [510]. Despite the clinical prevalence of polyradiculoneuritis, demonstration of inflammatory cell infiltrates in peripheral nerve biopsies (e.g., common peroneal nerve or tibial nerve sampled at the level of the stifle) seems to be very uncommon, as least in my experience. Undoubtedly, inflammation would be more frequently observed in nerve root biopsy samples. Idiopathic polyradiculoneuritis occurs infrequently in cats. As with dogs, demonstration of inflammatory cells in peripheral nerve biopsy samples from cats with clinical evidence of acute polyradiculoneuritis is unusual. Of all the feline peripheral nerves processed in my laboratory, I have seen only one case of polyneuritis in a cat with clinical signs suggestive of a polyradiculoneuritis. A severe, acute polyneuritis associated with anemia and transient icterus and fever was reported in a four year old neutered female cat [371]. Pathological findings were largely restricted to peripheral nerves and axons and consisted of extensive destruction of myelin and axons and macrophage infiltration. The variable presence of perivascular cuffs of lymphocytes and plasma cells was commensurate with an inflammatory disease and suggested a possible viral and/or immune-mediated etiology. Clinical signs included tetraparesis progressing to tetraplegia, lack of placing and tendon reflexes, depressed flexor reflexes, and hyperesthesia. Cranial nerves, perineal reflex and tail function were normal, as was mental status. Severe muscle wasting was present in all limbs after two weeks. EDX data were not available. Brain, spinal cord and nerve roots were not examined.

#### **Cauda Equina Polyradiculoneuritis -**

A polyradiculoneuritis has been reported in two dogs - a 9 year old female Labrador Retriever and an 8 month old female Yorkshire Terrier - that were presented with a lumbosacral syndrome (pelvic limb paraparesis, muscle hypotonia and atrophy, loss of patellar reflexes, and proprioceptive loss) [372]. Pain sensation, bladder function, and anal reflex were intact. Motor nerve conduction velocity was decreased in the sciatic-tibial nerves. Latency of F-waves was markedly increased following stimulation at the level of the greater trochanter and at the hock. Pathologically, lesions in both dogs were located in the lumbosacral nerve roots that comprise the cauda equina. Dorsal and ventral nerve roots, as well as dorsal root ganglia were involved. There was marked interstitial and perivascular infiltration of mononuclear cells (lymphocytes, plasma cells, and macrophages), axonal degeneration, demyelination, and remyelinating clusters. Milder changes were seen in nerve roots throughout the spinal cord, as well as in roots of the trigeminal nerve. Muscle changes reflected neurogenic atrophy. Intraneural injection of serum from an affected dog failed to induce demyelination in normal rat nerve. Serum levels of the myelin-specific protein, P2, were not elevated in either dog. Protein level in CSF was increased in one dog.

#### **Chronic Inflammatory Demyelinating Polyneuropathy -**

Over the past several years, we have accumulated data on a spontaneous demyelinating peripheral neuropathy that we have called chronic inflammatory demyelinating polyneuropathy (CIDP) [373]. Based on surveys of biopsies received from the Scott-Ritchey neuromuscular laboratory at Auburn University and from my private peripheral nerve laboratory, CIDP is one of the more common neuropathies seen in dogs and cats. This disorder occurs in dogs and cats of either gender and does not appear breed-related. Mature animals of any age may be affected (from 1 to 14 years). Onset of signs is usually insidious and the course is typically chronic, often relapsing, and frequently slowly progressive. Clinical signs are usually first noticed in the pelvic limbs and, in most animals, progress to involve the thoracic limbs. Clinical signs include tetraparesis, sometimes progressing to tetraplegia, stumbling gait, and hyporeflexia. Less commonly observed signs are muscle trembling (dogs), intermittent shifting limb lameness characterized by a plantigrade stance (cat), and ventroflexion of the head and neck (cat). Facial nerve paralysis or laryngeal paralysis are seen occasionally in dogs, while megaesophagus/regurgitation is found in some cats. Serological testing is normal, although one cat had an IgG monoclonal gammopathy. CSF analysis is usually normal, although occasional animals may show a moderate protein increase. Motor nerve conduction velocities (NCVs) are decreased, along with temporal dispersion, decreased amplitudes and prolonged latencies of the compound muscle action potentials. Slow sensory NCVs have also been noted. EMG studies in this report were either normal or revealed mild, patchy pattern of fibrillation potentials and positive sharp waves. Pathologically, changes in teased single fibers from peripheral nerves are dominated by multifocal paranodal demyelination, and sometimes segmental demyelination. Other changes include remyelination and variable numbers of fibers with internodal globules. Axonal degeneration is infrequently observed. Scattered, thinly myelinated fibers are seen on semithin sections. Severe changes may include presence of onion-bulbs and rarefaction of myelinated fibers. Ultrastructural studies reveal macrophages within myelinated fibers stripping the myelin sheaths, naked and remyelinating axons, and focal/multifocal endoneurial mononuclear cells, including lymphocytes, rare plasma cells, macrophages with myelin debris, and vacuolated fibroblasts.

Indirect immunofluorescence revealed positive IgG staining in peripheral nerve myelin sheaths from two dogs. No fluorescence was seen using anti-dog or anti-cat C3 (positive immunofluorescence to anti-human IgM and C3d was observed in control dog and cat nerve sections incubated with serum from a human patient with an IgM monoclonal gammopathy [374]). In skeletal muscle, minimal lesions are seen, apart from mild fiber size variation in some cases. Diagnosis is based on clinical signs, relapsing clinical history, and nerve biopsy studies. Prognosis is often favorable with treatment. The majority of dogs and cats (approximately 90%) were initially steroid-responsive (e.g., prednisolone at 1 - 2 mg/kg PO bid for at least a week followed by alternate day, reduced dosage for several weeks or several months), with many animals showing a return to normalcy following treatment. In some cases, the response to steroids is incomplete. Signs may relapse when treatment ceases (requiring additional treatment cycles) or upon reduction of the dose of steroids. Uncommonly, some animals with relapsing signs that are steroid-responsive may become steroid-resistant and deteriorate clinically.

The course of the disease, clinical signs, electrophysiology, and pathology have similarities to chronic inflammatory demyelinating polyneuropathy in people in whom weakness has a proximal distribution [262]. Most human patients with CIDP respond to corticosteroids and other immunosuppressive agents (e.g., azathioprine and cyclophosphamide), plasma exchange, and intravenous immunoglobulin (therapies aimed at treating immune-mediated disorders) [347]. Sporadic case reports of chronic relapsing polyradiculoneuritis in a dog [375] and a cat [376], chronic relapsing polyneuropathy in a cat [377], and prednisolone-responsive neuropathy in a cat [378], also appear very similar to CIDP.

### **Infectious Polyradiculoneuritis -**

A severe polyradiculoneuritis and/or polymyositis associated with either *Toxoplasma gondii* or *Neospora caninum* occurs commonly in dogs, especially those less than one year of age (see toxoplasmosis). In one dog with diskospondylitis due to *Aspergillus terreus*, multiple granulomas with fungal elements were found in the subarachnoid space associated with the nerve roots of the cauda equina [379].

### **Postvaccinal Polyradiculoneuritis**

Post-vaccinal polyradiculoneuritis (e.g., multivalent vaccine, inactivated rabies vaccine) has been reported only sporadically in dogs [380-382] with signs and clinical course similar to those in dogs with Coonhound paralysis. The condition, also known as postvaccinal inflammatory neuropathy (IPN), occurs rarely in people and is believed to be an autoimmune reaction triggered by the vaccine against some myelin, axonal or neuronal component [526].

### **Trigeminal Neuritis -**

Trigeminal neuritis, or idiopathic trigeminal neuropathy, occurs commonly in dogs and sporadically in cats and is typically characterized by acute onset of jaw paralysis, inability to close the mouth, drooling, and difficulty eating and drinking [383-385]. Older animals are usually affected, although the condition may occur at any age. There is no apparent breed, sex, or seasonal predisposition, although in one retrospective study of 29 cases, Golden Retrievers were overrepresented [518]. In this study, trigeminal sensory deficits were found in 9 of 26 dogs (35%). Horner's syndrome (due to damage of postganglionic sympathetic fibers incorporated in segments of the trigeminal nerve and its ophthalmic branch) has been observed in several cases [149,518,525], as well as occasional facial nerve involvement [518]. EMG studies usually reflect abnormalities in muscles of mastication and CSF studies may be abnormal (usually characterized by a mild mononuclear pleocytosis, often with normal or mildly elevated protein content) [518]. Pathologically, a bilateral non-suppurative neuritis has been found in motor branches of the trigeminal nerve and ganglion, associated with demyelination and occasional fiber degeneration, and accompanied by inflammatory infiltrates consisting predominantly of macrophages and B and T lymphocytes [149,525]. Masticatory muscle changes may reflect variable neurogenic atrophy, usually without evidence of inflammatory cell infiltrates. The disease appears to be self-limiting and recovery usually occurs in 3 to 4 weeks, but some cases may take several months to resolve. Corticosteroid administration appears not to affect the clinical course of the disease [518]. Supportive fluid and nutrient intake may be necessary. Definitive antemortem diagnosis of trigeminal neuritis is complicated by the fact that biopsy of the trigeminal nerve is difficult.

The severity of muscle atrophy, the clinical course, and clinical recovery may depend upon the extent of axonal degeneration present. If it is the dominant lesion, then prognosis can be guarded. Note that some animals with rabies may present with signs of trigeminal neuritis.

Definitive classification of this disorder awaits more detailed pathologic studies on a greater number of cases, although the few cases examined histologically are suggestive of immune-mediated disease [525]. I think that it is also possible that trigeminal neuritis in some instances may represent a focal manifestation of a more diffuse polyradiculoneuritis. Note that bilateral trigeminal neuropathy in a dog has been reported in association with lymphosarcoma [386], and an invasive intracranial juvenile parameningeal rhabdomyosarcoma that destroyed the trigeminal nerve causing unilateral denervation atrophy of masticatory muscles was reported in a 23 month old dog [530]. When I was at the Neuromuscular Diagnostic

Laboratory at Auburn University, many of the muscle samples that we received from dogs with suspected masticatory myositis (and some dogs with clinical evidence of trismus!) showed non-inflammatory neurogenic atrophy compatible with idiopathic trigeminal neuritis/neuropathy.

### **Rottweiler Distal Sensorimotor Polyneuropathy**

A polyneuropathy has been reported in mature Rottweiler dogs in the US [387]. Clinical signs are characterized by paraparesis that progresses to tetraparesis, spinal hyporeflexia and hypotonia, and appendicular muscle atrophy. While signs may appear acutely, the course tends to be gradually progressive (up to 12 months or longer in some dogs) and may be relapsing. Nerve and muscle biopsies were examined from eight affected Rottweilers, six male and two female, aged between 1.5 and 4 years. Pronounced neurogenic atrophy was present in skeletal muscle samples and there was no evidence of necrosis, phagocytosis or inflammation. Changes in sensory and motor peripheral nerves included loss of myelinated nerve fibers, axonal necrosis, and variable numbers of fibers with inappropriately thin myelin sheaths. Demyelination and remyelination were more apparent in dogs with a chronic clinical course. Regenerating clusters were not common. Ultrastructural findings included occasional myelinated fibers showing myelinoaxonal necrosis, demyelinated fibers often associated with macrophage infiltration, many axons with myelin-like membranous profiles, increased endoneurial collagen, occasional axonal atrophy, and numerous Büngner bands. Many axons had a watery appearance with loss of neurofilaments and microtubules, but no evidence of neurofilamentous accumulation. Onion-bulb formation was rare. Lesions in unmyelinated fibers included increased numbers of Schwann cell profiles and loss of axons in Schwann cell subunits. Morphological and morphometric studies indicated preferential loss of medium- (5.5 to 8  $\mu\text{m}$ ) and large-caliber (8.5 to 12.5  $\mu\text{m}$ ) fibers which was more severe in distal parts of nerves compared to more proximal regions and nerve roots. Mean nerve fiber diameters for proximal and distal segments were  $4.95 \pm 2.75 \mu\text{m}$  and  $2.41 \pm 0.71 \mu\text{m}$ , respectively. Numerous positive sharp waves and fibrillation potentials were detected in appendicular muscles by EMG, especially in muscles distal to the elbow and stifle. Few abnormal potentials were noted in proximal limb/paraspinal muscles. Motor and sensory nerve conduction velocities were reduced in some dogs. Hematology, blood chemistries, spinal radiography/ myelography were normal. With the exception of one dog that was serologically positive for Valley Fever and *Ehrlichia canis* (1:80), and another dog that was antinuclear antibody positive (1:160), testing has been negative for immunological disorders (e.g., lupus erythematosus cell preparation, rheumatoid factor, Coombs' test), endocrine dysfunction (e.g., diabetes mellitus, hypothyroidism, hyperadrenocorticism), toxicity (e.g., lead, cholinesterase levels), and infectious disease (e.g., Rocky Mountain Spotted Fever, Borreliosis, ehrlichiosis). CSF protein was marginally elevated in one dog. Pathological findings suggest this condition is a dying-back, distal sensorimotor polyneuropathy. Prognosis appears guarded to poor; despite the fact that some dogs showed a temporary response to corticosteroid therapy. This disorder has morphological and morphometric similarities to hereditary sensory and motor neuropathy (HSMN) type II (or CMT II) in people, a distal axonal neuropathy with normal or near normal nerve conduction velocities with reduced amplitudes, indicating loss of axons [43,225].

Note that this condition appears similar to other distal symmetrical polyneuropathy seen in large-breed dogs.

### **Sensory Neuropathies**

Several sensory neuropathies have been observed in small animals, primarily in dogs. In people, sensory neuropathies may affect one or more sensory modalities - pain, proprioception, touch, and temperature. In animals, only the first two sensory modalities can be determined with any degree of accuracy [388]. Sensory neuropathies in dogs may also be characterized by self-mutilation. In general, paresis and muscle atrophy are not present, and no abnormal spontaneous potentials are detected on electromyographic testing. Nerve conduction studies may demonstrate slowed velocities in sensory but not motor nerves. Spinal cord dorsum potentials (a type of spinal cord evoked potential) can also be used to accurately assess functional severity and distribution of abnormalities in proximal sensory nerves, dorsal nerve roots, and spinal cord dorsal horns in dogs with suspected neuropathy, radiculopathy, or myelopathy involving the brachial or lumbosacral intumescences [86,389]. Electrodiagnostic (EDX) evaluation of H-reflexes (H-waves) provides additional information on dorsal nerve root integrity/function [388].

### **Sensory Ganglioradiculitis -**

A sensory disorder has been reported in adult dogs (with an age range from 1.5 to 9 years) of different breeds and of either gender [353,390-394]. I have also seen the condition in a 2.5 year old Scotch Collie. The terms *sensory neuronopathy*, *sensory polyganglioradiculoneuritis*, and *ganglionitis* have also been used to describe this condition because of involvement of craniospinal sensory ganglia. Pathologically, the disease is characterized by pronounced degeneration and loss of neurons in dorsal root ganglion cells and in cranial sensory ganglia (such as trigeminal and nodose ganglia), usually accompanied by inflammatory lymphoplasmacytic and macrophage infiltration. The infiltrating cells are primarily T lymphocytes and immunoglobulins are not present on the cell membranes of affected neuron [522]. A marked loss of larger-diameter



myelinated fibers has been observed in dorsal roots and in sensory nerves, and there may be selective loss of myelinated fibers in the dorsal columns of the spinal cord (grossly, the dorsal columns may appear white/opaque), indicative of degeneration secondary to ganglion dysfunction [200,392]. Similar degenerative changes may occur in sensory pathways of cranial nerves, such as the spinal tract of the trigeminal nerve and the solitary tract (containing visceral afferent fibers of facial, glossopharyngeal and vagus nerves). In one case I have seen, axonal necrosis present in multiple nerves was more severe distally. Ventral roots are usually spared or only mildly affected. Denervated Schwann cells of myelinated and unmyelinated fibers are found in the dorsal roots.

The clinical course is usually insidiously progressive over several months or years. Clinical signs are variable and include proprioceptive deficits, generalized ataxia with preservation of muscle strength, depression or absence of tendon reflexes, such the patellar reflex, facial hypalgesia/paresthesia, megaesophagus, head tilt, loss of voice, hearing loss, anisocoria, difficulty in prehending food, dysphagia, stiff gait often with hypermetria, and occasionally, self-mutilation. Muscle atrophy is usually not a feature; however, atrophy of masticatory muscles may be seen in some dogs, attributed to inflammatory involvement of fibers from the motor root of the trigeminal nerve as they course through the trigeminal ganglion [390]. Hematological values, CSF analysis and radiographic studies are within normal limits; however, a mild increase in CSF cellularity and total protein may be present. EMG findings are usually normal. Sensory nerve conduction velocities (NCVs) are slowed or absent, while motor NCVs are normal. Prognosis is guarded to poor. To date, corticosteroids (e.g., prednisone) and procarbazine have been ineffective.

The pathogenesis of ganglioradiculitis remains to be established, but the evidence points to a cell-mediated immune mechanism [522]. A possible toxic etiology was considered in a 4 year old Labrador Retriever with pathology localized to sensory nerves, dorsal root ganglia and the dorsal columns of the spinal cord [393]. In this dog, liver mercury levels were elevated above normal, although below the range normally associated with mercury poisoning.

### **Progressive Axonopathy in Boxers -**

This putative sensory neuropathy is an inherited autosomal recessive neuropathy of Boxer dogs [395-402]. Pathological findings are seen in nerve roots, peripheral nerves, and in the CNS. Large axonal swellings (spheroids) are found in various brainstem nuclei, especially cuneate and superior olivary nuclei. Spheroids and degenerating fibers are seen in spinal cord white matter, particularly in lateral and ventral funiculi. Minimal changes occur in the dorsal columns. The optic pathways are also involved. In the PNS, small axonal swellings develop at proximal paranodal areas in dorsal and ventral nerve roots as well as in proximal nerves. Axonal swellings are due to accumulation of both disorganized neurofilaments and membranous organelles, mainly vesicles and vesiculo-tubular profiles. Myelin over such swellings is often attenuated. Myelin changes predominate in the nerve roots, whereas axonal degeneration and regeneration are encountered in more distal nerves. In contrast, regenerating axonal clusters are common in cervical ventral roots, throughout the course of the disease. Axonal degeneration in the spinal cord shows no obvious tract or proximal/distal selectivity [397]. Most early axonal spheroids are surrounded by a myelin-associated glycoprotein (MAG)-positive zone but in the larger swellings and longer duration cases this was sometimes absent; however, distorted Schmidt-Lanterman incisures, a feature of the advanced disease, tend to be strongly MAG-positive. [402]. It has been hypothesized that failure of slow axonal transport may occur in roots leading to axonal swellings and secondary hypoplasia of more distal, larger-diameter fibers. Myelin/Schwann cell alterations might occur in response to the axonal changes [399,400]. Immunocytochemical studies revealed that the major axonal cytoskeletal proteins in nerve roots and in spinal cord are markedly disturbed: many spheroids contain increased amounts of actin, and sometimes deficient tubulin in the periphery of the neurofilament accumulations, while the distribution of axonal fodrin in CNS and PNS appears unaltered [401]. In addition, the perikarya of many motor neurons in the spinal cord and brain stem contained phosphorylated 200 kD neurofilaments (phosphorylated neurofilaments are normally localized in the axon rather than the cell bodies).

Onset of clinical signs occurs about 2 months of age. There is a progressive ataxia and weakness, initially in pelvic limbs, but later involving thoracic limbs. Proprioceptive function, muscle tone and tendon reflexes are diminished or absent, while pedal reflexes and pain sensation are preserved. Absent patellar reflexes can be detected at 1 month of age. Muscle atrophy is minimal. Signs slowly progress until animals are 12 to 18 months of age, and then tend to stabilize. Mild cerebellar signs may be evident late in the course of the disease. EDX studies reveal little spontaneous activity in muscle but reduced motor and sensory nerve conduction velocities and reduced evoked muscle action potential amplitudes after about 4 months of age. Eventually, sensory nerves cease to conduct impulses. F-wave latency is increased.

Diagnosis is suggested by signalment, clinical, and electrodiagnostic data, and confirmed by nerve biopsy or pathological evaluation of the CNS. Prognosis is poor. There is no treatment.

A disorder with similar clinical signs, clinical course, and pathological features has been reported in a young Rottweiler puppy (2 affected puppies out of a litter of 11) [200]. Distribution and nature of lesions observed in a 5 month old Pyrenean Mountain dog were also considered similar to those in the Boxers [403], although the characteristic axonal neurofilamentous accumulation was not described.

### **Sensory Neuropathy in Long-Haired Dachshunds -**

This is a neurological disease reported in Long-Haired Dachshund puppies thought to be inherited as an autosomal recessive trait [120,404]. The pathogenesis is unknown. Pathological findings occur in distal sensory nerves affecting both larger caliber myelinated fibers and unmyelinated fibers (UF). Changes include myelinated nerve fiber loss, axonal degeneration, many bands of Büngner, marked increased numbers of axonal organelles (mitochondria, smooth endoplasmic reticulum, and glycogen), prominent endoneurial fibrosis, occasional evidence of small regenerating clusters, and rarely, onion bulb formations. While UF density appeared normal, abnormalities in UFs were frequently seen in distal nerves including increased numbers of intra-axonal neurotubules and/or tubulo-vesicular elements, stacks of lamellar profiles, collections of dense granular material, along with accumulation of mitochondria, smooth endoplasmic reticulum and glycogen, darkening of the axoplasm, empty Schwann cell subunits, Büngner bands, and collagen pocket formations. Paranodal demyelination seen on teased nerve preparations is considered to be secondary to axonal changes. Degenerative changes are noted in the vagus nerve. Less severe, but similar changes occur in mixed nerves. Sensory neurons in the spinal ganglia are normal and dorsal roots appear normal. In the CNS, distal degeneration has been observed in the fasciculus gracilis, suggesting this condition is a distal central-peripheral axonopathy.

Clinical signs are noted in dogs as early as 8 to 12 weeks of age, and are characterized by subtle ataxia, loss of proprioception and placing reactions, especially in pelvic limbs, reduction or loss of pain sensation ("nociception") over the whole body in response to superficial and deep pain stimulation, and dribbling of urine. Self-mutilation of the penis and intermittent vomiting have been noted. Pelvic limbs may splay-out when dogs are lying in sternal recumbency. There is no evidence of paresis or muscular atrophy and patellar reflexes are normal or slightly reduced. EMG studies and motor NCVs are normal. Sensory NCVs are reduced or absent.

Diagnosis is based on signalment, clinical, electromyographic and pathological (nerve biopsy) data. Provided that complications do not occur from vomiting or from self-mutilation (which may necessitate muzzling), it has been stated that most affected dogs live normally [388]. There is no treatment. This canine disorder was considered to have some similarities to human hereditary sensory neuropathy type II (now re-classified as hereditary sensory and autonomic neuropathy type II, an autosomal recessive disorder).

A sensory neuropathy having similar clinical (loss of proprioception and generalized loss of superficial pain sensation, except over the lips and inside the nostrils where pain sensation was blunted but present, and urinary incontinence) and pathological features has been reported in a 2 month old Border Collie puppy [405]. Sensory nerve action potentials were absent.

Another condition that appears similar to that in the Dachshunds has been reported in a 6 year old, male Jack Russell Terrier presented with a chronic history of abnormal pelvic limb posture and a tendency to repeatedly bite its right pelvic limb [406]. At rest, the dog stood with one pelvic limb flexed and the other extended. Neurological examination revealed proprioceptive deficits in pelvic limbs and in one thoracic limb. Postural reaction testing was clumsy in pelvic limbs. The dog continued to dribble urine following micturition. Pain perception was diminished in the distal pelvic limbs up to the level of each stifle. Patellar reflexes were brisk bilaterally and there was no evidence of paresis or muscle atrophy. Electrodiagnostic data were not included in this report. Examination of a sensory nerve biopsy (lateral branch of the superficial peroneal nerve) revealed absence of myelinated fibers, preservation of unmyelinated fibers, abundant endoneurial and epineurial connective tissue, and small numbers of denervated Schwann cells. Future studies are needed to determine if there is involvement of sensory ganglia, and if the condition is inherited.

### **Sensory Neuropathy in English Pointers -**

This sensory neuropathic disease, inherited as an autosomal recessive trait, has been reported in English Pointer dogs [407-409]. An apparently similar, recessively inherited entity has been reported in Czechoslovakian Shorthair Pointer dogs in Europe and has been called toe necrosis, hereditary neurotrophic osteopathy, and ulcero-mutilating acropathy [410]. Changes in the primary sensory neurons are observed pathologically, including presence of small spinal ganglia with reduced numbers of cell bodies (from 20 - 50%), a disproportionately large population of small sensory cell bodies, degeneration of unmyelinated and myelinated fibers in the dorsal roots and peripheral nerves, and reduced fiber density and myelin staining in the dorsolateral fasciculus (Lissauer's tract) of the spinal cord in which pain and temperature fibers travel. Ultrastructurally, there is evidence of bands of Büngner, denervated Schwann cell subunits, collagen pockets, lysis of neurotubules and filaments in unmyelinated fibers, and little evidence of axonal regeneration of myelinated or unmyelinated fibers [407].

The pathogenesis of this disease is presently unclear; however a deficiency in growth and/or differentiation of primary sensory neurons may be involved. The loss of primary sensory neurons is associated with a notable reduction in staining of substance P, an excitatory agent that mediates nociception (i.e., pain sensation) [411]. This loss is most apparent in the dorsolateral fasciculus and superficial laminae of the spinal dorsal horns. In older dogs, a loss of P substance was also found in the spinal nucleus of the trigeminal nerve. This finding, in addition to appearance of scattered fiber degeneration in the

dorsal columns of the mature Pointer, suggested that fiber degeneration may progress slowly with age to include sensory systems not affected in early postnatal life [411].

Clinical signs are characterized by nociceptive (pain) loss and acral mutilation. This nociceptive loss is more apparent in distal parts of limbs, so that acral analgesia is replaced by hypalgesia proximal to the carpus and tarsus. No nociceptive loss is found about the face. Although blunting of digital pain has been detected prior to weaning, clinical signs usually become apparent at 3 to 8 months when affected dogs suddenly begin to lick and bite their paws. Acral changes include swollen reddened paws, ulcerations, lacerations, paronychia, painless fractures, and autoamputations.

There is no evidence of proprioceptive loss, ataxia, or depressed tendon reflexes. EMG studies and sensory and motor nerve conduction studies are normal. Diagnosis is based on signalment and clinical data, and normal electrodiagnostic results. Histopathological evaluation of nerve or spinal ganglia biopsy samples may support the clinical diagnosis. Prognosis is poor because of high potential for osteomyelitis secondary to autoamputation. There is no treatment for the underlying sensory neuropathy.

This sensory neuropathy appears to have clinical and pathological similarities to several of the hereditary sensory and autonomic neuropathies (types I through V) described in people [43,412].

### **Sensory Trigeminal Neuropathy -**

Sensory trigeminal neuropathy has been reported in a 2 year old, female Rough Coated Collie dog [413]. The cause was not determined. Pathological lesions included marked loss of nerve fibers in the trigeminal nerves and their spinal tracts. Motor fibers of the mandibular nerves were unaffected. These changes were not associated with inflammation and were considered to be secondary to loss of neurons in the trigeminal ganglion (Gasserian ganglion). The motor nucleus of the fifth nerve was normal. Clinical signs of acute onset of excessive salivation, coughing and dysphagia were believed to be associated with bilateral loss or absence of tactile sensation and deep pain from the face, tongue and oral mucosa. The condition in this dog remained relatively unchanged over an 18 month period.

### **Idiopathic self-mutilation -**

Idiopathic self-mutilation or behavioral self-mutilation has been seen in both dogs and cats. Affected animals are often of nervous or high-strung breeds such as Siamese, Burmese, Himalayan or Abyssinian cats, and Doberman Pinscher, German Shepherd, Great Dane, and Irish Setter dogs [414]. In dogs, this self-mutilation may manifest itself as continued licking, biting or scratching of one or more areas usually near the carpus or hock, and has been termed *acral lick dermatitis* (ALD), *lick granuloma*, *acral pruritic nodule*, *neurodermatitis*, and *canine obsessive/compulsive disorder* (also see Behavioral disorders). EDX studies have provided evidence of both mild sensory axonal polyneuropathy in some affected dogs [415], as well as apparent motor ventral root involvement in 9 of 16 dogs with lick granuloma [416]. The tricyclic antidepressant drug, clomipramine (Anafranil®), dosed at 1 to 3 mg/kg PO daily, results in significant improvement in the dogs' licking behavior [417-419]. Other effective drugs against ALD include citalopram, fluoxetine, and naltrexone [420-422].

A feline orofacial pain syndrome has been described in cats (the majority of cases are in Burmese cats) characterized by acute onset of exaggerated licking and chewing movements with pawing at the mouth sometimes leading to severe self-mutilation [517]. Signs may be seen in kittens around 14 weeks of age (associated with vaccination and mouth ulceration), in kittens around 5 months of age (associated with teething), or in older cats (from 1 to 16 years of age), sometimes associated with stress or dental disease. The attacks can be episodic (eg, lasting between 5 minutes and 2 hours) or continuous (necessitating paw bandaging or an Elizabethan collar to prevent mutilation). Some cats show spontaneous remissions and recurrences. The syndrome may be similar to trigeminal neuralgia and glossodynia (burning or painful tongue) in people. Treatment using anti-epileptic drugs (diazepam or phenobarbitone) are effective in many cases.

I have seen degenerative changes in sensory and in mixed nerves (perhaps affecting only the sensory portion) from 2 dogs (an 8 month old male Spitz and a 6.5 year old male Miniature Doberman Pinscher) presented for bilateral self-mutilation of the digits in the pelvic limbs. Axonal necrosis was dominant in the Spitz, whereas, demyelination and remyelination were the main features seen in the Miniature Doberman. Mild dorsal column pallor (fasciculus gracilis) was observed in the Spitz (suggesting this condition might have been a form of sensory ganglioradiculitis), but no inflammation was present in dorsal roots or ganglia in which there was mild loss of neurons. No spinal cord or ganglia changes were noted in the Miniature Doberman. Neurological examination and EMG testing were normal in both dogs, while sensory but not motor nerve conduction velocity was markedly reduced in the Miniature Doberman.

Self-mutilation has also been noted in animals with nerve injury, e.g., lumbosacral stenosis and trauma [423,424], and auto-mutilation was observed in an epizootic of tibial and peroneal neuropathy in a kennel of Walker Hound puppies thought to be toxin-induced (see toxic neuropathies) [425].

## Storage Disease Neuropathies

Readers are referred to Chapter 2 and Storage Diseases for neuropathies associated with different storage disorders, including gangliosidosis, fucosidosis, globoid leukodystrophy, glycogenosis type IV, mannosidosis, and sphingomyelinosis (phenotypic variant of Niemann-Pick disease type A).

## Toxic Neuropathies

Clinically-related, drug-induced neuropathies are not well defined in dogs and cats. Vincristine-associated peripheral neuropathy was reported in a 12 year old, female, Golden Retriever that received 16 weekly doses of vincristine (0.5 mg/m<sup>2</sup>) as part of a regimen for treatment of mycosis fungoides [426]. The dog was presented for sudden onset of a shuffling pelvic limb gait, intermittent collapse, and difficulty negotiating turns and stairs. Neurological examination revealed mild ataxia in the pelvic limbs, depressed pelvic limb postural reactions, and depressed patellar and pelvic limb withdrawal reflexes. EMG testing revealed fibrillation potentials and positive sharp waves consistent with denervation. Sciatic motor NCV was decreased. Evoked muscle potentials were polyphasic and had reduced amplitude and prolonged duration. Severe nerve fiber degeneration, nerve fiber loss (both small- and large-caliber fibers), and marked endoneurial fibrosis were seen in a nerve biopsy sample. The neuropathy improved after vincristine was discontinued. Results of a repeat nerve biopsy taken 10 weeks after cessation of vincristine administration showed fewer degenerating nerve fibers and presence of demyelination-remyelination. The dog appeared neurologically normal at this time. In experimental studies in cats, focal axonal swellings (giant axon formations) due to distorted accumulations of neurofilaments and secondary paranodal demyelination were found primarily in the proximal portions of peripheral nerves, with only a few giant axon formations seen distally along with variable axonal degeneration [427]. In people, a neuropathy typically occurs in all patients receiving vincristine for a sufficient period and signs/EDX testing suggest a symmetrical distal sensorimotor polyneuropathy [105]. Loss of myelinated fibers and axonal degeneration in unmyelinated fibers have been observed [428]. In people, itraconazole may aggravate vincristine-induced neurotoxicity [429,430]. Cis-platinum, another antineoplastic agent, has been implicated in peripheral neuropathies in human patients, usually resulting in large fiber sensory neuropathy and axonal degeneration/demyelination [431,432]. The neurotoxicity is dose-limiting and cumulative. Neurological signs (ataxia, lower motor neuron paresis in pelvic limbs) have been noted in some dogs following use of this drug, although a distinction between toxic neuropathy and paraneoplastic neuropathy was not made [433].

As chemotherapeutic treatment of tumors becomes more aggressive, there is a real possibility that clinicians will be presented with further cases of drug-induced neuropathies. There is also a risk of neuropathies being induced by tumor irradiation (see radiation therapy). In an experimental study of intraoperative radiation therapy, peripheral neuropathy resulting from direct effects of irradiation on nerve and secondary effects on nerve vasculature was apparent clinically (e.g., hind limb paresis associated with significant loss of large-caliber nerve fibers and endoneurial/perineurial/epineurial fibrosis) 1 to 19 months following irradiation [434,435]. This toxicity appears to be dose-limiting, with intraoperative doses < 15 Gy not resulting in clinically significant peripheral nerve injury [436,437]. The nerve toxicity appears to be enhanced by hyperthermia [438].

Thallium poisoning, from ingestion of thallium-containing rodenticides or insecticides, may produce degenerative changes in peripheral nerves (distended myelin sheaths with swelling and fragmentation of axons) and ganglionitis, with clinical signs of trembling, muscle spasms, paresis or paralysis of hind limbs, severe pain, and megaesophagus [439]. Experimental studies in cats indicate that thallium induces a central-peripheral sensory distal axonopathy [440]. Thallium in rodenticides has been banned in the US since 1965; however, sporadic cases of acute and chronic thallium poisoning continue to be reported [441,442] (see thallium). Experimental neuropathies (resulting in dying-back disorders) have been induced in cats using a variety of neurotoxic hexacarbons and acrylamide [443]; however, these neuropathic toxicities are rarely encountered in clinical practice. Neurotoxic organophosphates may induce a delayed peripheral neuropathy in cats (16 - 18 days after injection) associated with focal, distal but not terminal axonal degeneration [444] (see organophosphate/carbamate toxicity). Experimental administration of beta, beta'-iminodipropionitrile (IDPN) to cats induces neurofilament-filled axonal swellings in proximal and distal regions of peripheral nerves [445]. Lead intoxication does not appear to produce a toxic neuropathy in dogs [446] (see lead poisoning). Experimental pyridoxine (vitamin B6) intoxication in dogs results in degeneration of primary sensory neurons (affecting peripheral nerves, dorsal roots, dorsal funiculus, and spinal tract of the trigeminal nerve) and clinical signs of ataxia-dysmetria and proprioceptive deficits [447-449]. Iatrogenic peripheral vestibular disease and/or deafness may result from use of various antibiotics and chemical agents that cause degeneration of vestibular and auditory peripheral receptors (see deafness and vestibular disease).

An epizootic of peroneal and tibial neuropathy was reported in a kennel of Walker hounds in eastern North Carolina [425]. Approximately 40 puppies were involved. Signs of pelvic limb monoparesis, areflexia, muscle atrophy, and deficient postural reactions, were first seen in 2 week old puppies. Signs progressed to severe paresis and self-mutilation of digits. Limb analgesia was also noted. Histopathological findings were largely restricted to distal tibial and peroneal nerves and included nerve fiber loss, especially the larger-caliber fibers, and occasional scattered demyelinating fibers.

Ultrastructurally, axonal neurofilaments were often whorled and denser than normal. Dilated granular endoplasmic reticulum were prominent in Schwann cell cytoplasm. The cause was not determined; however, a toxic-induced neuropathy secondary to a contaminant in the well water was suspected.

### **Traumatic Neuropathy**

Trauma to peripheral nerves is a common cause of neuropathies in animals [450]. Nerve injuries may result from mechanical blows, gunshot wounds, fractures, pressure, and stretching (see brachial plexus avulsion). Sciatic nerve injury in dogs and cats often follows fracture of the iliac body or acetabulum, or from sacroiliac fracture-dislocation with cranial displacement of the ilium [424,451-453]. Facial nerve injury may occur during total ear canal ablation and lateral bulla osteotomy in the dog [454]. Bilateral mandibular nerve injury has been reported in dogs thought to result from carrying large objects in the mouth (probably from mandibular nerve neuropraxia, see below) [455]. A transient facial nerve paralysis (presumably resulting from nerve compression) was reported in a 50 kg Doberman Pinscher x Great Dane dog following prolonged anesthesia [168]. Neck trauma in cats may lead to Horner's syndrome and subclinical ipsilateral laryngeal hemiplegia by damage to the vagosympathetic trunk [294]. Sciatic nerve entrapment by muscle or fibrous tissue has been reported in small animals following femoral fracture, ischial or acetabular fracture, and femoral head and neck excision [452,456-458]. Bilateral entrapment was found in a dog with hip dysplasia [457]. Note that nerve root entrapment and compression commonly occur in dogs with cauda equina syndrome (see lumbosacral stenosis). Another common cause of nerve compression and/or entrapment is peripheral nerve neoplasia (see peripheral nerve tumors). In cats with hyperlipidemia, peripheral nerve fascicles are subjected to compression by xanthomata which leads to secondary axonal degeneration and nerve fiber loss. Nerve root injury and spinal cord hemorrhage has been reported in a dog in association with tearing of the dura mater following an episode of violent struggling [459].

Additional iatrogenic causes of nerve injury include crushing, cutting, compression by casts or splints, and injecting agents into, or adjacent to the nerve. In one study involving 57 dogs and 26 cats with femoral fractures that were fixed with intramedullary pins, 12 (14.5%) exhibited signs of sciatic nerve entrapment [460]. Normograde intramedullary pinning of the femur is less likely to induce sciatic nerve injury, particularly in midshaft and distal fractures [461]. In an experimental study evaluating the effects of injection of various agents normally administered intramuscularly, the degree of nerve injury varied with [462,463]:

- a. The agent injected; e.g., iron-dextran, meperidine, and cephalothin induced minimal damage, while maximal nerve injury followed injection of penicillin, diazepam, chlorpromazine, and steroid agents (especially hydrocortisone and triamcinolone, while minimal damage was seen with dexamethasone) [462].
- b. The site of injection, e.g. severe injury followed intrafascicular injection but there was minimal injury following extrafascicular injection.
- c. The quantity of drug injected.
- d. The caliber of the fibers, e.g., large, heavily myelinated fibers were more susceptible to injection injury than smaller, thinly myelinated nerve fibers.

The mechanism of injury appears to be a direct neurotoxic effect on both axons and Schwann cells, with disruption of the blood-nerve barrier and with changes occurring in nerves within 30 minutes of injection [464,465].

Nerve damage may be defined in terms of structural damage. *Neurotmesis* is complete severance of all structures of the nerve with Wallerian degeneration (axonal necrosis and myelin fragmentation) of the distal stump. *Axonotmesis* consists of damage to the nerve fibers resulting in degeneration; however, the endoneurial and Schwann cell sheaths remain intact and provide a framework for axonal regeneration. *Neuropraxia* is an interruption in the function and conduction of a nerve without structural damage.

The regenerative ability of a nerve is directly proportional to the degree of continuity of connective tissue structures within the nerve. In neuropraxic and axonotmesic lesions where the endoneurial connective tissue and Schwann cells remain intact, the potential for axonal regeneration is good. In neurotmesis, axonal regeneration is usually frustrated by lack of connective tissue scaffold or growth tubes. Also, scar tissue tends to interfere with sprouting axons, resulting in neuroma formation. Once an axon has grown past the point of injury and penetrates a Schwann tube in the distal nerve stump, remyelination occurs. Axonal regeneration occurs at a rate of 1 to 4 mm per day. Clinical signs of spinal nerve dysfunction are outlined in Table 2.

<b>Table 2. Clinical Signs of Spinal Peripheral Nerve Trauma</b>			
<b>Nerve</b>	<b>Spinal Cord Origin</b>	<b>Muscles Innervated</b>	<b>Clinical Signs of Dysfunction</b>
Suprascapular	C6 - C7	Supraspinatus Infraspinatus	Loss of shoulder extension; muscle atrophy with prominent spine of scapula
Axillary	C7 - C8	Deltoideus Teres major Teres minor	Reduced shoulder flexion; deltoid atrophy; reduced sensation over lateral surface of shoulder
Musculo - cutaneous	C6 - T1	Biceps brachii Brachialis Coracobrachialis	Reduced elbow flexion; loss of bicipital reflex; reduced sensation over medial surface of forearm
Radial	C6 - T2	Triceps brachii Extensor carpi radialis Ulnaris lateralis Lateral digital extensor Common digital extensor	Reduced extension of elbow, carpus, and digits; loss of extensor postural thrust and limb support (with radial nerve damage above the elbow); loss of triceps reflex; reduced sensation over dorsal surface of paw and craniolateral surface of forearm
Median	C7 - T2	Flexor carpi radialis Superficial digital flexor	Reduced flexion of carpus and digits; reduced sensation over palmar surface of paw
Ulnar	C8 - T2	Flexor carpi ulnaris Deep digital flexor	Reduced flexion of carpus and digits; reduced sensation over caudal surface of forearm
Femoral	L4 - L6	Iliopsoas Quadriceps Sartorius	Inability to extend stifle or bear weight on affected limb; loss of patellar reflex; reduced sensation over medial surface of paw, hock, stifle, and thigh (via sensory saphenous nerve)
Obturator	L5 - L6	External obturator Pectineus Gracilis	Inability to adduct hip or thigh (animal "does the splits" on a smooth surface)
Sciatic	L6 - S1	Biceps femoris Semimembranosus Semitendinosus	Inability to flex stifle; loss of flexor reflex (for other dysfunction see branches of sciatic nerve - tibial and common peroneal nerves)
a) Tibial	(L6) L7 - S1	Gastrocnemius Popliteus Deep digital flexor Superficial digital flexor	Inability to extend hock or flex digits; reduced sensation over plantar surface of paw; loss of gastrocnemius reflex
b) Common Peroneal	L6 - L7 (S1)	Peroneus longus Lateral digital extensor Long digital extensor Cranial tibial	Inability to flex hock or extend digits; knuckling of dorsal paw; reduced sensation over craniodorsal surface of paw, hock, and stifle
Pudendal	S1 - S3	External anal sphincter Striated urethral muscle	Loss of anal reflex and bulbocavernosus reflex (males only); reduced sensation of perineum
Pelvic (parasympathetic)	S1 - S3	Smooth muscle of bladder and rectum	Urinary incontinence

Modified from Braund KG. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994 [16].

Diagnosis of traumatic neuropathy is usually based on history and clinical signs. EDX data may be helpful in evaluating nerve integrity, severity of damage, and in monitoring progress/regeneration. Approximately 5 to 7 days post-injury are required before increased insertional activity and spontaneous potentials (e.g., positive sharp waves and fibrillation

potentials) are detected. Nerve integrity may be easily assessed by nerve stimulation proximal and distal to the site of the lesion. Exploratory surgery is another method for direct evaluation of peripheral nerve damage. Treatment may involve surgical anastomosis (neurorrhaphy) or neurolysis (freeing of a nerve from inflammatory adhesions). Experimental studies in dogs suggest that too early mobilization following neurorrhaphy will impede nerve regeneration by delaying revascularization and enhancing scar formation [466]. In those instances where nerve damage is chronic, high, or severe, muscle relocation and muscle tendon transfers are recommended, including arthrodesis of the tibiotarsal joint in pelvic fracture cases where the lumbosacral joint or sciatic nerve is severed [424,456,467]. Prognosis is guarded with peripheral nerve injury. Lesions characterized by neuropraxia and axonotmesis have a better prognosis than those of neurotmesis. Also, the closer the nerve injury is to the muscle it must reinnervate, the better the prognosis. Self-mutilation that results from abnormal sensation in an affected area produced by regeneration of sensory nerves can be a major complication and a poor prognostic sign. In one study involving 34 dogs and cats with nerve injury associated with fracture-dislocation of the pelvis, 81% had good/excellent limb function 16 weeks after the injury, and the outcome was the same for animals with or without surgery [424]. The authors of this report suggested that surgery be performed on animals with signs of severe pain or moderate to severe nerve injury so as to relieve the nerve entrapment, avoid further nerve damage, and assess prognosis (e.g., the affected nerve may be severely attenuated, frayed, stretched, lacerated or transected). Loss of limb function or self-mutilation occurred in 15% of animals in this study. A poor prognosis is given if limb function has not improved in 3 to 4 months in animals with lumbosacral trunk/high sciatic nerve injury [424]. Physical therapy, such as a whirlpool bath, may help to overcome circulation problems and delay muscle atrophy (see rehabilitation).

### **Vascular Neuropathy**

Readers are referred to chapter 2 and Myopathic Disorders for a review of vascular neuropathy (see ischemic neuromyopathy).

### **Vestibular Disease**

Various forms of vestibular disease have been identified in dogs and cats, and they may involve peripheral receptors within the inner ear or the centrally located nuclei and tracts within the brainstem.

A. Peripheral Vestibular Disease may be congenital, idiopathic, or associated with otitis media-interna. There are also several miscellaneous causes of peripheral vestibular disease.

Idiopathic Vestibular Disease - This is an acute peripheral vestibular syndrome, without evidence of inflammatory lesions, that is seen in cats of all ages and in older dogs [468,469]. In one study of 75 affected cats, 80% were diagnosed in the months of July and August [468]. Both dogs and cats have signs of peripheral vestibular involvement including head tilt, asymmetrical ataxia, and horizontal or rotatory nystagmus. More severe signs of falling, rolling, and vomiting (especially in dogs) are seen occasionally. The signs appear suddenly, often causing severe incapacitation. In a few days, the affected animal tends to stabilize and improves gradually over several weeks. Residual deficits, such as a mild head tilt, may be seen. It is important to exclude an infection as the cause since the idiopathic syndrome and acute labyrinthitis (see below) have identical clinical signs; however, facial nerve dysfunction and Horner's syndrome are never seen in animals with idiopathic disease. In the idiopathic disease, the external, middle, and inner ear are grossly normal. Otoloscopic and radiographic examinations are normal. The canine disease must also be differentiated from brain stem disease (e.g., central vestibular disease). The syndrome has also been mistaken for an acute vascular accident (i.e. infarction or hemorrhage) of the brain stem. The signs of the idiopathic syndrome are only those of peripheral vestibular dysfunction. Postural reactions and other cranial nerves are not affected. In the early stages, postural reactions may be very difficult to test and the peripheral nature of the syndrome may not be obvious until the second or third day.

The peracute onset of clinical signs and absence of otitis media/interna, based on otoscopic and or radiographic examinations, suggest a diagnosis of idiopathic vestibular disease. Analysis of CSF is normal. The etiology remains uncertain. No microscopic lesions have been documented in the labyrinth, vestibular nerve and ganglion, or within the brainstem.

Prognosis for spontaneous remission is good; however, recovery may take 2 or 3 weeks. Recurrences may be noted, especially in dogs. A variety of treatments have been tried, including antibiotics, anti-inflammatory agents, anti-motion sickness drugs, and others. There is no evidence that any treatment alters the course of the disease. If infection cannot be absolutely excluded, antibiotics are recommended, but aminoglycosides should be avoided.

Otitis Media-interna refers to an inflammation of the middle and inner ears and is a common cause of peripheral vestibular dysfunction in dogs and cats [468]. The most common route of infection to the middle and inner ears is from the external ear

canal with attendant otitis externa and subsequent rupture of the tympanic membrane. The nasopharynx is also a source of retrograde infection by way of the eustachian tubes. A third source of infection of the middle-inner ear structures is hematogenous spread. Most infections are caused by bacteria including *Staphylococcus* sp., *Streptococcus* sp., *Proteus* sp., *Pseudomonas* sp., *Enterococcus* sp., and *Escherichia coli*. Foreign bodies such as grass awns may initiate inflammation and predispose to secondary microbial infection. Yeast (e.g., *Candida* sp. and *Malassezia canis*) and fungal infection (e.g., aspergillosis, cryptococcosis) [470,471] are observed infrequently. Animals predisposed to chronic otitis externa and chronic ear mite infestations would appear to have an increased risk of developing otitis media-interna; however, in one survey, no breed was disproportionately represented, compared to the hospital population examined [468]. Nevertheless, the psoroptid mite *Otodectes cynotis* reportedly can damage the tympanic membrane and invade the middle and inner ears, especially in cats, resulting in secondary infection of these structures [472]. Occasionally, middle ear infection occurs secondary to trauma (e.g., traumatically ruptured tympanic membrane associated with petrosal bone fracture), inflammatory polyps, granulomas (e.g., cryptococcal), and tumors (see below).

Varying degrees of vestibular disturbance reflect otitis media-interna. Signs may range from ipsilateral head tilt, nystagmus (frequently rotatory), positional strabismus (ventral or ventrolateral), and ataxia of trunk and limbs, such as torticollis, circling, falling, and rolling. These dramatic signs may become less pronounced within 2 - 3 days. Postural reactions, preservation of strength, and initiation of voluntary movement are similar to those described for idiopathic vestibular disease. Mild hypertonia and hyperreflexia may occur in limbs on the side of the body opposite the vestibular lesion. Pain may be noted around the external ear and when the animal opens its mouth. An aural discharge, sometimes bloody, head shaking, and pawing or rubbing of the ears may be noted. Frequent yawning has been observed and affected animals may be lethargic, anorexic and febrile. Attendant middle ear inflammation may disturb function of the facial and sympathetic nerves which course through the middle ear, resulting in ipsilateral facial paresis/paralysis and Horner's syndrome, respectively. During the course of the disease, irritation of the sympathetic fibers may induce mydriasis. Since the facial nerve contains the parasympathetic preganglionic neurons that modulate lacrimal gland secretion, animals with otitis media-interna may have decreased tear production and develop ipsilateral keratitis sicca. Facial nerve dysfunction may be seen in approximately 50% of animals with otitis media/interna [473]. Ipsilateral hemifacial spasms have been reported in dogs with otitis media [186] and signs, including blepharospasm, elevation of the ear, and deviation of the nose, are probably due to facial nerve irritation. Another structure that may be involved in otitis media-interna is the cochlear nerve, dysfunction of which results in deafness.

Occasionally, otitis media-interna is bilateral and affected animals may assume a wide-based stance with head close to the ground and swinging from side to side, or alternatively, assume a crouched posture on the ground with limbs spread apart [89]. Nystagmus is not present and the oculocephalic response (normal vestibular nystagmus) is absent in bilateral disease. Such animals may also be deaf and show bilateral facial paralysis.

The diagnosis of otitis media-interna is based on clinical signs, otoscopic examination, radiography/imaging, and surgical exploration [474]. Examination of the pharynx (visually or using a retroflexed pediatric gastroscope) may reveal inflammation that may have spread to the middle ear via the auditory tube [472], polyps originating from the auditory tube or tympanic cavity [475], or granulomas protruding from the choanae [470]. Cats with tumors of the middle and inner ear often have signs of pain when opening the mouth [182]. Otoscopy may reveal an otitis externa and evidence of erosion or rupture of the tympanic membrane. Fluid in the middle ear produces outward bulging of the tympanic membrane which may appear opaque and hyperemic. Fluid behind the membrane may appear clear or discolored. Fluid and/ or inflammatory exudate should be sampled for culture, cytology, and sensitivity testing from the external and middle ear by aspiration if the tympanic membrane has ruptured, by myringotomy (surgical incision of the tympanic membrane performed caudal to the malleus in the posteroinferior quadrant of the tympanic membrane [472]), or by exploratory surgery. Radiographic examination (recommended skull radiographic views include oblique lateral, open-mouth and ventrodorsal projections [472] of the petrous temporal bones may reveal middle ear inflammation as suggested by fluid density and sclerosis of the bulla. Normal detail of the bony labyrinth may be lost. The presence of a nasopharyngeal mass on lateral radiographic views is suggestive of inflammatory polyps in cats [182]. Lysis or active periosteal reaction involving the bulla or petrous part of the temporal bone is usually associated with neoplasia. In some instances, radiographs may be normal, despite significant middle ear inflammation [474] and special imaging techniques, e.g., CT and MRI may be more sensitive in detection of fluid in the middle ear disease [476]. Soft tissue changes in the early stages of the disease may be detected better with MRI [477]. Positive contrast ear canalography is considered to be a more sensitive method for detecting tympanic membrane rupture and otitis media than either otoscopy or survey radiography [478].

Prognosis is usually favorable with prolonged oral and topical antibiotics chosen from positive culture and sensitivity studies. When culture and sensitivity are not available, chloramphenicol (25 - 50 mg/kg PO tid in dogs and bid in cats), cephalexin (22 mg/kg PO tid); cefadroxil (22 mg/kg PO bid) or trimethoprim-sulfadiazine (15 mg/kg, PO or SC bid) can be used, over a 4 to 6 week period. For cases of cryptococcal peripheral vestibular disease (e.g., *Cryptococcus neoformans*), itraconazole at 50 to 100 mg PO every 24 hours for several months has been beneficial in cats [470]. Artificial tears can be



used for animals with keratitis sicca. Because of potential ototoxicity, especially in cases where the tympanic membrane has been damaged, topical agents (e.g., iodophors, aminoglycosides, cetrimide, iodine, chloramphenicol and chlorhexidine) should be used with caution. Indeed, topical antibiotics are considered insufficient for the treatment of otitis media-interna [476]. Drainage of the middle ear using a bulla osteotomy (e.g., from a ventral approach) may be required in the event of fluid buildup in the tympanic bulla. Note that the tympanic bulla in cats consists of dorsolateral and a ventromedial cavities divided by an incomplete bony septum, and both compartments should be surgically drained [479]. In more chronic cases refractory to treatment, surgical debridement and total ear canal ablation-lateral bulla osteotomy or ventral osteotomy (especially used for disease processes confined to the middle and inner ear) can be successfully performed [181,182,480]. Short-term complications may include Horner's syndrome, facial nerve paralysis, and otitis interna [182]. In some animals, neurological signs may recur, while in other patients, minor residual neurological deficits (e.g., head tilt or ataxia) may persist. Ventral bulla osteotomy and curettage, along with removal of retained epithelium and debris, can successfully treat cases of recurrent otitis media that develop after total ear canal ablation and lateral bulla osteotomy [481]. Removal of nasopharyngeal polyps by traction and/or bulla osteotomy is usually successful [475]. Treatment of middle ear tumors may involve surgical resection, radiation or chemotherapy. Prognosis is guarded to poor [182,482].

Additional potential complications include development of osteomyelitis of the osseous bulla and petrous temporal bone, extension of infection to the meninges or brain parenchyma leading to meningoencephalitis [89] or to pontine and cerebellomedullary abscesses [483], complications that occurs more often in cats [484], and cholesteatoma formation. A cholesteatoma is a form of epidermoid cyst that is lined by stratified squamous keratinizing epithelium. It appears as a laminated structure composed of layers of keratin, and rests on a fibrous stroma of inflammatory granulation tissue. In one study of otitis media, 7 of 42 dogs had an accompanying cholesteatoma within the middle ear [47]. In this study, the masses appeared to be formed from pockets of the tympanic membrane which became adherent to the inflamed middle ear mucosa. Clinical signs in some affected dogs included head tilt, poor balance, deafness, and difficulty and pain when eating or yawning. None of the dogs had Horner's syndrome or facial nerve disorder. Radiographically, the cholesteatomas were sometimes responsible for extensive resorption and remodeling of adjacent bone, including the temporomandibular joint and retrogenoid process. Treatment is by surgical resection (e.g., via osteotomy).

Congenital Vestibular Disease - Signs of peripheral vestibular disease without deafness have been observed in several breeds of puppies [89,485,486] including English Cocker Spaniels, German Shepherds, Tibetan Terriers, and in Burmese kittens. Signs may be noted from birth to 3 or 4 months of age, and typically include a pronounced head tilt, circling, and often falling and/or rolling. Nystagmus is not a feature in these young animals. The cause of this disorder is unknown. Pathological studies have failed to produce any evidence of either inflammation, degeneration or malformation. Prognosis is guarded since clinical signs may regress completely, recur, or remain static. There is no treatment.

A congenital condition, characterized by early onset of deafness and vestibular disease, has been reported in Doberman Pinscher puppies [57]. Twenty-one dogs from ten different litters were examined for signs of vestibular disease, at ages between birth and 10 weeks. Signs included rolling or falling, head tilt, circling, and inaccurate control of head movements with occasional bumping against objects. Vision was normal and no head tremors were observed. As the puppies grew older, signs usually became less pronounced and affected animals showed only mild head tilt and a tendency to circle when excited; however, relapses occasionally occurred. Vestibular testing (such as rotational and post-rotational nystagmus, and caloric stimulation) was abnormal in all dogs, bilaterally. Righting reflexes were poor in young dogs, but improved with age. Hearing, as assessed by the brainstem auditory evoked response (BAER) method, was absent in all puppies 3 weeks of age or older. Otoscopic and radiographic studies indicated that the tympanic membranes and tympanic bullae were normal. Histopathologic studies revealed that all affected dogs had a non-inflammatory neuroepithelial degeneration of the cochlea with a progressive loss of the auditory sensory hair cells, resulting in almost complete loss of the organ of Corti by 11 weeks of age. Microscopic examination of the vestibular system from several affected dogs showed either absence of otoconia or some degree of otoconial abnormality in one or more maculae. Pedigree analysis indicated that this vestibular/hearing disorder in Doberman Pinschers had an autosomal recessive mode of inheritance.

Diagnosis is usually straightforward and the prognosis for clinical improvement of the vestibular disease is good. This improvement may result from central compensation due to sensory and visual input. However, the deafness is severe, bilateral, and permanent. While hearing is very difficult to assess accurately using response to sounds, such as clapping, BAER testing can provide early diagnosis of deafness, allowing breeders and owners to identify affected parents and avoid further breeding.

A similar condition has been seen in Beagle and Akita puppies and in Siamese kittens [89]. Almost identical clinical signs have been reported in two related litters of Doberman Pinscher puppies with congenital peripheral vestibular disease attributed to lymphocytic labyrinthitis [487]. Multiple lymphocytic aggregates were found in the lamina propria beneath the ciliated columnar epithelium of the middle ear. No lesions were found in the brain. Analysis of CSF was normal. Signs of unilateral or bilateral vestibular disease developed when puppies were between 3 and 12 weeks of age. Several of the

puppies were deaf and some showed thoracic limb hypermetria. Vestibular signs improved in some dogs but persisted unchanged in others.

Congenital nystagmus, without vestibular disease, occurs sporadically in puppies. The nystagmus is usually pendular and spontaneously resolves. It has also been seen in Belgium Sheepdogs with incomplete development of the optic chiasm [488]. Nystagmus may also be observed in some Siamese cats and it may persist for life [89]. It has also been seen in some cats with Chediak-Higashi syndrome in which it is associated with congenital cataracts, photophobia, pale irises, and albinotic or depigmented fundi [489].

Miscellaneous Causes of Peripheral Vestibular Disease - Neoplasia is an infrequent cause of peripheral vestibular disease, however, older cats and dogs appear at risk for tumors involving the middle or inner ear [182]. While a variety of tumors, including anaplastic carcinoma, lymphoblastic lymphosarcoma, osteosarcoma, fibrosarcoma, chondrosarcoma, squamous cell carcinoma, basal cell tumors, sebaceous adenocarcinoma, papillary adenoma, and ceruminous gland adenoma and adenocarcinoma have been reported in dogs and cats (involving bony or soft tissue structures), squamous cell carcinoma and ceruminous gland adenocarcinoma may be the most common tumor of the middle ear in cats [490,491]. In dogs, however, papillary adenomas and extension of adnexal or ceruminous gland tumors originating in the external ear appear to be more common in this location [492]. Rarely, middle ear tumors may directly extend into the brainstem [482]. Neurofibromas involving the vestibulocochlear nerve are very rare. Prognosis is poor. Iatrogenic peripheral vestibular disease may result from use of aminoglycoside antibiotics, which can cause degeneration of vestibular and auditory peripheral receptors (see deafness). Cats are especially susceptible to the vestibular effects of streptomycin. Cranial trauma may cause signs of peripheral vestibular disease secondary to fractures in the petrous temporal bone or tympanic bulla. Signs of peripheral vestibular disease accompanied by facial paresis/paralysis, but without otitis media, occur sporadically in dogs, a few of which have had hypothyroidism and pituitary chromophobe adenoma [89]. Thyroid hormone replacement therapy has been ineffective in these cases.

Inflammatory Polyps are another cause of peripheral vestibular disease. Polyps are smooth, non-neoplastic masses that arise from the lining of the tympanic cavity, auditory tube, or nasopharynx [490,493]. They are typically pedunculated and fixed by a thin stalk to their point of origin. The polyps are often associated with obstructive disease and may cause rupture of the tympanic membrane. Inflammatory polyps are commonly associated with otitis media [475]. They are thought to occur as a result of chronic middle ear infection or from ascending infection from the nasopharynx. Polyps tend to be single masses and are especially common in young adult to middle-aged cats, with no apparent gender or breed predisposition. They are infrequently observed in dogs [494]. Clinical signs include head shaking, aural discharge, head tilt, facial paralysis, vestibular dysfunction, Horner's syndrome, and sometimes, presence of a mass in the external ear canal. Masses in the nasopharynx may cause dysphagia and stertorous respiration, respiratory distress, and phonation change [490,495]. Polyps are composed of fibrous connective tissue stroma containing numerous capillaries and inflammatory cells, including macrophages, neutrophils, lymphocytes and plasma cells, covered by pseudostratified columnar ciliated or non-ciliated respiratory epithelium. This epithelium is continuous with the tympanic cavity, eustachian tube and nasopharynx. Some polyps are covered by squamous epithelium if lesions originate from deeper portions of external ear canal. Focal mucosal ulceration may be seen. They are differentiated from neoplastic masses by direct visualization, cytology and histopathology. Skull radiographs may indicate changes similar to those seen in otitis media. They may also be seen as soft tissue masses in the pharyngeal region and within the tympanic bulla. Imaging (e.g., CT) can also be used to define the regional extent of the polyp [496]. Treatment is usually uncomplicated and involves simple traction-avulsion of the mass through the external meatus (sometimes necessitating lateral ear canal resection) or from the nasopharynx (retraction of the soft palate or incision may be required to visualize the eustachian tube). Bulla osteotomy facilitates polyp removal from the tympanic bulla. Prognosis is usually good, although a temporary Horner's syndrome was commonly observed in one study following bulla osteotomy [475]. Less frequently, self-limiting facial and hypoglossal neuropathies may also develop following surgery [521]. Recurrences can occur. In one study, recurrence rate following removal by traction-avulsion was approximately 40% and was more likely in cats with aural polyps and in those with more severe aural signs. Interestingly, none of the cats treated with prednisolone after traction-avulsion suffered a recurrence. Results of another study suggest that traction-avulsion is a reasonable treatment for inflammatory polyps if the bullae are radiographically normal [523].

B. Central Vestibular Disease - Signs of central vestibular disease in animals are similar to those seen with peripheral vestibular disease. However, in central disease, there may be evidence of other cranial nerve dysfunction due to involvement of various brainstem nuclei (e.g., trigeminal or abducent), altered mental status, vertical or positional nystagmus, cerebellar signs, and evidence of paresis and/or proprioceptive deficits resulting from brainstem involvement of descending and ascending long tracts. Also, animals with central vestibular disease have a tendency to roll in one direction [89]. Central signs do not include Horner's syndrome but facial paresis/paralysis, secondary to involvement of the facial nucleus, may be observed. Unilateral lesions in the brainstem usually produce an ipsilateral hemiparesis and postural reaction deficiencies

(associated with lesions in the general proprioceptive and/or upper motor neuron systems). However, central lesions occasionally result in a "paradoxical" vestibular syndrome in dogs in which the lesion is located on the opposite side to that expected from the clinical signs (head tilt, strabismus, body tilt). The lesion, typically a space-occupying one in the area of the cerebellopontine angle, such as tumor or granulomatous mass, is considered to be located on the same side of the body in which proprioceptive/postural reaction deficits are detected [89,497-499,529]. Presumably, presence of unilateral deficits of other cranial nerves would be another indicator of the side on which a lesion is located. This syndrome may occur if vestibular pathways in either the caudal cerebellar peduncle (particularly the supramedullary juxtarestiform body) or the flocculonodular lobe of the cerebellum are involved [89,498]. The paradoxical vestibular syndrome occurs less frequently in cats [500,501].

Causes of central vestibular disease include inflammatory diseases, such as distemper and granulomatous meningoencephalomyelitis (GME), bacterial meningitis/meningoencephalitis [502] and rickettsial meningoencephalitis (e.g., Rocky Mountain spotted fever) [503], feline infectious peritonitis [504], toxoplasmosis and neosporosis, migrating parasites, such as *Cuterebra* larvae in cats [89], and mycotic meningoencephalomyelitis (e.g., cryptococcosis and *Acremonium* sp. [505], along with vascular disease, thiamine deficiency (especially cats), storage diseases [506], trauma, drug toxicity (e.g. metronidazole in dogs and cats) and tumors, particularly those located at the cerebellopontine angle. Surface tumors may include meningioma, choroid plexus papilloma, medulloblastoma, neurofibroma, trigeminal neurofibrosarcoma/schwannoma, and lymphosarcoma [89,529]. Dogs may be at risk for meningiomas and choroid plexus papillomas, while in cats, meningiomas and lymphomas are common [89,476]. Parenchymal tumors that may cause central vestibular dysfunction include the focal/neoplastic form of GME, gliomas, or metastatic tumors [89,507]. Forebrain tumors may result in central vestibular disease secondary to caudal transtentorial herniation [476].

Diagnostic aids in evaluating central vestibular disease include otoscopy, CSF analysis for inflammatory diseases (including cellularity, protein, antibodies, protein electrophoresis, etc.), advanced imaging studies (e.g. CT or MRI) for tumors, skull radiographs for skull fractures and tympanic bulla evaluation, BAER studies to evaluate hearing and integrity of central brainstem pathways, and surgical biopsy/resection (intracranial, ear canal, or bulla osteotomy) [473,476,508]. Specific treatments are based on the underlying cause of the vestibular disorder, for example antimicrobial therapy for infectious agents, surgical removal/resection, radiation therapy and chemotherapy for tumors, and thiamine administration for thiamine deficiency.

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## Endogenous Metabolic Disorders (6-Feb-2003)

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Endogenous metabolic disorders in small animals that impact the central nervous system (CNS) encompass myriad conditions, including electrolyte abnormalities, endocrine disorders, and organ failure. These conditions have sometimes been referred to as metabolic encephalopathies because of functional CNS perturbations arising from altered energy metabolism, destabilization of neural membranes, hypoxia, endogenous toxin formation, or osmolality shifts.

An outline of this chapter is as follows:

### **Diabetes Mellitus**

### **Hepatic Encephalopathy**

### **Hypernatremia**

### **Hypocalcemia**

### **Hypoglycemia**

### **Hyponatremia**

Central Pontine Myelinolysis

### **Hypothyroidism**

Myxedema Coma

### **Uremic Encephalopathy**

### **Miscellaneous Metabolic Disorders**

Acidosis

Alkalosis

Hyperthyroidism

Hypophosphatemia

Hypercalcemia

Potassium Disorders

### **Diabetes Mellitus**

This chronic disorder is associated with impaired utilization of carbohydrates and enhanced lipid and protein use.

Neurological signs attributable to the CNS have been associated with two hyperglycemic syndromes: diabetic ketoacidosis (DKA) and nonketotic hyperosmolar hyperglycemia (NKH). Hyperglycemia results in hyperosmolality and this may lead to cerebral dehydration, with a pathogenesis similar to that of hypernatremia.

Insulin deficiency (either relative or absolute) is the problem in patients with DKA and is related to the hyperglycemia associated with increased gluconeogenesis, enhanced glycogenolysis, and reduced glucose clearance [1], associated with increased levels of diabetogenic hormones (epinephrine, glucagon, cortisol, and growth hormone) which promote insulin resistance [2-4]. Furthermore, there is increased fatty acid mobilization and fatty acid oxidation (from increased glucagon:insulin ratio), and as a result, elevated serum ketone bodies (e.g., acetoacetic acid and beta-hydroxybutyric acid) from lipolysis. Glycosuria ensues once renal threshold is exceeded, e.g., > 180 - 220 mg/dl in dogs and > 200 - 320 mg/dl in cats [3], leading to osmotic diuresis, polyuria and compensatory polydipsia. Increasing serum levels of ketones will also eventually exceed renal tubular threshold and spill into the urine exacerbating the already existing osmotic diuresis and water loss from hyperglycemia, and potentiate loss of sodium, potassium and magnesium in urine. In summary, the consequences of DKA are severe metabolic acidosis, hyperosmolality, osmotic diuresis, dehydration, and severe electrolytic derangement [2,5,6]. In patients with NKH, sufficient insulin is produced to prevent lipolysis and ketone body formation, although insufficient to prevent hyperglycemia. This syndrome is seen when blood glucose > 600 mg/dl (sometimes > 1000 mg/dl) and with hyperosmolality > 330 - 350 mOsm/kg [4,5]. Compromised renal function (from primary renal disease or

from the hypovolemia) with decreased glomerular filtration and decreased excretion of glucose may be associated with the extreme hyperglycemia and hyperosmolality [3,5,7]. Neurological signs for both DKA and NKHH are essentially the same as those seen in patients with hyponatremia. In addition, DKA animals are dehydrated and may have a fruity acetone breath odor from the ketosis. In people, seizures are commonly observed in patients with NKHH [8-10], possibly related to excessive activation of glutamate receptors ("excitotoxicity"), including N-methyl-D-aspartate receptor-operated channels [11]. Diagnosis is based on biochemistry panels, serum osmolality, anion gap determination, and blood gas studies [5,12]. Demonstration of both hyperglycemia and glucosuria is an important diagnostic finding, and most dogs and cats with DKA have evidence of hyponatremia [3]. Treatment consists of administration of the following [3,5]:

- a. 9% saline solution at 60 - 100 mL/kg/24h. In addition, provide 80% of fluid deficits (% dehydration x kg body weight = fluid deficit in liters) and also adjust for any ongoing fluid losses (e.g., vomiting and diarrhea) to correct cellular dehydration and hypovolemia. For initial fluid replacement, isotonic saline administration at a moderate rate is recommended over hypotonic fluids given rapidly since a rapid decrease in serum osmolality may lead to cerebral edema (especially in patients in whom the serum concentration of sodium fails to rise as that of glucose declines) [4,13]. In one human study, failure of the serum sodium concentration to rise as glucose concentration declined was considered to be a marker for excessive administration of free water [14]. In this report, repair fluid containing an average of 125 mEq/L sodium early in therapy usually prevented a downward trend in the concentration of sodium in serum thereby avoiding a rapid decline in effective serum osmolality [14]. Rehydration over 48 hours was shown to be a safe strategy in people with moderate or severe DKA [15]. After 12 to 24 hours, fluids can be changed to 0.45% saline if hyponatremia or hyperchloremia are present [5].
- b. Potassium or phosphate supplementation if required (if unknown, add 20 mEq KCl and 20 mEq KPO<sub>4</sub> to each liter of fluids). During therapy for DKA, serum potassium levels decline in most animals due to rehydration (dilution effect), correction of acidosis (hydrogen moves out of cells in exchange for potassium), insulin-induced cellular uptake of potassium, and continuing urinary losses [16]. Hypokalemia may lead to muscle weakness, cardiac arrhythmias and respiratory failure. Hypophosphatemia occasionally occurs in animals with DKA and has been reported in association with osmotic diuresis and urinary losses. It can lead to muscle weakness, hemolysis, rhabdomyolysis, seizures, cardiac dysfunction and respiratory failure [17]. When serum phosphate levels < 1.0 mg/dl, potassium phosphate at 0.01 - 0.03 mmol phosphate/kg/h should be administered for 6 hours [5,18].
- c. Bicarbonate supplementation if serum bicarbonate < 12 mEq/L or total venous CO<sub>2</sub> < 12. Amount of bicarbonate (mEq) = body wt (kg) x 0.4 x (12 - patient's serum bicarbonate level). Note that improved renal perfusion will facilitate urinary loss of ketoacids while insulin treatment will decrease the production of ketoacids.
- d. Insulin therapy, e.g., regular crystalline insulin at 0.2 U/kg, IM followed by 0.1 U/kg IM hourly until blood glucose level < 250mg/dL, then use SC regular insulin at 0.1 - 0.4 U/kg every 6 - 8 hours. Note that resolution of ketoacidosis requires insulin therapy.
- e. Dextrose supplementation using 5% dextrose (e.g., add 100 ml of 50% dextrose to each liter of fluids) once blood glucose level falls below 250 mg/dl to avoid hypoglycemia.

Note - For more detailed information on therapeutic management of animals with severe diabetic ketoacidosis, readers are referred to the recent publication by Nelson [3]. The overall aim should be to return to normal all abnormal parameters slowly over 36 to 48 hours. Too-rapid correction might lead to cerebral edema [2]. Since DKA usually coexists in dogs and cats with other conditions (e.g., pancreatitis, congestive heart failure, infection, gastroenteritis, renal failure, or insulin antagonistic disorders such as hyperadrenocorticism), treatment should also be directed at these disorders [3,16,18]. For animals with NKHH, primary treatment is aimed at rehydration (e.g., using 0.9% saline at 20 - 30 ml/kg IV as an initial bolus, and then 0.45% saline at 60 ml/kg/day), followed by insulin therapy (see above), and correcting any underlying illnesses including cardiac abnormalities, renal disease, or hyperthyroidism [4]. It is recommended that approximately one-half of the estimated body fluid deficits be corrected over the first 24 hours and the remainder over the ensuing 24 hours [5]. It has been stated that insulin should not be initiated until the patient has received hypotonic fluids for approximately 6 hours to avoid inducing cerebral edema (from rapid decrease in serum glucose) and hypokalemia (insulin induces movement of potassium from the extracellular space to the intracellular space) [5]. Finally, seizures associated with hyperglycemia (usually in NKHH patients) are resistant to anticonvulsant treatment and respond best to insulin and rehydration [1]. Note that besides the two hyperglycemic syndromes, a third diabetic emergency may occur in dogs and cats, namely insulin overdose, resulting in hypoglycemia. The clinical and neurological signs may be similar in all three instances [4]. In people, diabetes also increases the risk of stroke associated with large, medium, and small vessel atheroma formation, as well as arteriolar and capillary microangiopathy [1].

## Hepatic Encephalopathy

Hepatic encephalopathy (HE) in dogs and cats is a complex metabolic disturbance of the CNS that may result from diminished hepatic function, urea cycle enzyme deficiency, or shunting of portal blood around the liver. As a result, the metabolic and detoxification functions of the liver are impaired and/or bypassed and the unaltered constituents of the portal blood go directly into the systemic circulation. Many "toxic" substances derived from intestinal degradation, including ammonia, amino acids (especially the aromatic amino acids phenylalanine, tyrosine, and tryptophan), short-chain fatty acids, mercaptan and various biogenic amines, indoles and skatoles, have been incriminated in causing HE [19,20]. Ammonia, metabolized by astrocytes to glutamine (catalyzed by an astroglia-specific enzyme, glutamine synthetase [21]), has been one of the most studied toxins and is considered to play an integral role in the pathogenesis of HE [1]. Increased intracellular osmolality from too-rapid glutamine accumulation may result in cerebral edema, which also may play a role in development of cerebral hyperemia and increased intracranial pressure in experimental studies of fulminant hepatic failure [22]. Low-grade cerebral edema has been reported in humans with hepatic cirrhosis [23]. Glutamine, short-chain fatty acids, aromatic amino acids, and mercaptans are sodium/potassium ATPase inhibitors [1,24]. Other theories pertaining to the pathogenesis of HE include perturbed monoamine neurotransmission as a result of altered plasma amino acid metabolism; an imbalance between excitatory amino acid neurotransmission mediated by glutamate, and inhibitory amino acid neurotransmission mediated by gamma-aminobutyric acid; and increased cerebral concentration of an endogenous benzodiazepine-like substance [25-27]. It has been stated that there is no evidence that increased levels of "false" neurotransmitters (e.g., octopamine and phenylethanolamine), potentially leading to reduced neuronal excitation and increased neural inhibition, are responsible for the encephalopathy [1].

HE can occur with the conditions listed below.

1. Acute liver failure. Acute hepatic failure may occur in animals of any age. Causes may include toxic injury, metabolic disturbance (e.g., lipidosis in cats), trauma, heatstroke, vascular compromise (e.g., vena cava syndrome or liver lobe infarction), and infectious disease (e.g., infectious canis hepatitis) [28]. The onset of signs is rapid with a fulminant course. Non-specific signs may include depression, anorexia and vomiting.
2. Chronic liver insufficiency (e.g., chronic hepatitis, cirrhosis, hepatobiliary neoplasia, etc.) and acquired portal systemic shunting. Dogs with encephalopathy associated with chronic liver disease are typically middle-aged or older. Weight loss, depression, anorexia, gastrointestinal signs, polydipsia and polyuria may be observed. In these cases, acquired shunts may develop as a compensatory response to portal hypertension and appear as multiple tortuous vessels that usually communicate with the caudal vena cava. Rarely, multiple acquired extrahepatic shunts may develop as a consequence of portal hypertension associated with intrahepatic arterioportal fistulae in young dogs [29]. A syndrome resembling idiopathic noncirrhotic portal hypertension has been reported in 4 young Doberman Pinschers [30]. This hepatopathy, in which there is no intrahepatic arteriovenous fistulae, portal vein atresia or intrahepatic fibrosis, results in portal hypertension, development of portosystemic collateral vessels and HE. Abdominal ultrasonography disclosed a small liver and portosystemic collateral vessels. Radiographic imaging studies confirmed hepatofugal portal circulation. Histopathological features included increased cross-sectional views of hepatic arterioles, hepatic lobular atrophy, mild increase in connective tissue around some large portal triads, with absence of inflammation, disturbed lobular architecture, bile duct proliferation, or intrahepatic cholestasis. Acquired portosystemic shunting is uncommon in cats [240].
3. Congenital portosystemic anomalies (usually single shunts that may be intrahepatic or extrahepatic and usually not associated with portal hypertension) that shunt portal blood around the liver, allowing mesenteric blood to directly enter the central venous system, most frequently the caudal vena cava or azygous vein [31,32]. The congenital extrahepatic shunts usually involve the portal vein or one of its tributaries, such as the left gastric vein, splenic vein, cranial or caudal mesenteric veins, or gastroduodenal vein [31]. It has been reported that intrahepatic portosystemic venous anomalies are diagnosed relatively infrequently in dogs [33]. These shunts occur when the fetal ductus venosus remains patent or when another portal-to-hepatic-vein communication exists. Shunts tend to be extrahepatic in small breeds, while a single intrahepatic shunt is most common in medium-to-large breeds [34,35]. Congenital portosystemic anomalies usually occur in young dogs less than 1 year of age [36]. There are reports of breed predilection for congenital portosystemic anomalies, including Miniature Schnauzers, Yorkshire Terriers, Cairn Terriers, Australian Cattle dogs, Old English Sheepdogs, and Maltese Terriers [19,32,34,37,38]. Affected animals are often stunted and in poor nutritional condition. Clinical signs are intermittent, varying from one day to the next, and are frequently seen a few hours after eating a high protein meal. Signs may include anorexia, depression, weight loss, polydipsia/polyuria, jaundice, and ascites [32]. There may be intolerance to certain drugs, such as tranquilizers or anesthetics. Neurological signs (see below) reportedly occur in approximately 95% of cases with shunts [39]. In animals with congenital shunts the liver is grossly small and often mottled in appearance, while microscopic findings

include small hepatic acini with few portal venous branches and arteriolar hyperplasia [32,40]. Marked irregular thickening of the glomerular capillary wall has been observed in dogs with congenital shunts [41]. It has been reported that almost all Irish Wolfhound pups without signs of HE have moderate hyperammonemia and that approximately 2 - 3% of these dogs have inherited portosystemic shunts associated with high venous ammonia concentrations ( $>125\text{ }\mu\text{g/dl}$ ) and signs of HE [42].

4. Hepatic urea cycle enzyme deficiency. Affected dogs are usually less than 1 year of age and the HE is associated with hyperammonemia without any evidence of hepatocellular destruction or portosystemic shunting [19].

Irrespective of the cause, the neurological signs of HE are similar and are especially related to the prosencephalon (forebrain). Moderately severe cases can be characterized by alterations in behavior or personality, including staring into space, inappropriate vocalizing, aggression, and agitation. More severe changes can induce ataxia, circling, aimless wandering, and head pressing. Advanced neurological alterations can cause depression, blindness, myoclonus, stupor, coma, or seizures.

There are no gross CNS changes in animals with HE. Histopathological findings typically consist of diffuse polymicrocavitation of myelin (status spongiosus) at various levels of the brain, especially in the cerebral cortex (usually involving the peripheral fibers of the corona radiata at the junction of the gray matter), but cerebellum (e.g., cerebellar medulla and peduncles) and brainstem may also be involved, including the internal capsule, thalamus, and hypothalamus, pons, and medulla oblongata). The distribution tends to be bilaterally symmetrical and myelinated bundles of fibers interspersed with gray matter are typically prominent [40]. In the spinal cord, vacuolation occurs in the fasciculus proprius along gray and white matter borders [43]. Ischemic neuronal degeneration of the cerebral cortex has also been reported [44]. The vacuolation is considered to be cytotoxic edema [40] and may be associated with the hyperammonemia since the vacuoles tends to regress when blood ammonia concentration returns to normal (see comments on ammonia and cerebral edema, above) [45]. Experimentally, the vacuoles appear to represent ballooning of myelin sheaths which have split at the intraperiod line [46]. Another morphological feature of HE is presence of Alzheimer type II astrocytes which are most numerous in the neocortex, basal nuclei, and hippocampus. These cells, thought to be derived from protoplasmic astrocytes and characterized by their large, vesicular nuclei, may be in close association with neurons or isolated in the neuropil [40]. Glial fibrillary acidic protein (GFAP) staining is weak or negative, but S-100 expression is retained suggesting that HE results in selective loss of GFAP filaments [40,47]. Polyneuropathy has sometimes been reported in humans with HE [48], some cases of which are associated with alcoholism [49]. Note that polyneuropathies (in people) can develop secondary to liver disease-related vitamin E deficiency [50].

Acute hepatic failure is characterized by marked elevations in alanine aminotransferase (ALT) and total bilirubin, with variable levels of serum alkaline phosphatase (SAP). Chronic liver disease or cirrhosis is typified by variable levels of ALT and total bilirubin, with marked elevations in SAP. Liver enzyme levels can be normal or mildly elevated in animals with congenital shunts. Hypoproteinemia, hypoalbuminemia, hypoglycemia, hypocholesterolemia, and prolonged clotting times can be found in animals with impaired hepatic function, regardless of etiology [32]. Sulfobromophthalein (BSP) retention is often increased, blood urea nitrogen may be abnormally low (due to the inability of the liver to convert ammonia to urea), blood ammonia levels are often increased (approximately 90% of HE patients have an elevated fasting blood ammonia level, e.g.  $>95\text{ }\mu\text{g/dl}$  [19]), which may result in the presence of ammonium biurate crystals in the urine sediment from 50 to 100% of affected dogs [34,51]. Fasting (e.g., 12-hour) and post-prandial (e.g., 2-hour) total serum bile acid (TSBA) values are sensitive indicators of hepatic dysfunction, including occult liver disease such as portosystemic venous anomalies or hepatic cirrhosis [52-54]. Results of one study in dogs with suspected liver disease showed that fasting TSBA levels  $>20\text{ }\mu\text{m/L}$  and post-prandial TSBA values  $>25\text{ }\mu\text{m/L}$  were 100% specific for liver disease [55]. While TSBA levels do not indicate the severity of the hepatic disease or suggest a prognosis [53], comparison of fasting and post-prandial TSBA may help to discriminate between some hepatobiliary diseases (e.g., animals with significant extrahepatic or intrahepatic shunting often have normal or mildly elevated fasting TSBA) [56]. Another diagnostic aid regarded as being equal in sensitivity to postprandial SBA in dogs with shunts is the ammonia tolerance test [52]. Increased free cortisol levels have been reported in dogs with portosystemic shunts and HE [57]. In order to confirm the type of liver pathology present, hepatic biopsy is necessary. Clinicopathological features reported in young dogs with a syndrome resembling idiopathic noncirrhotic portal hypertension included erythrocyte microcytosis, normal to mildly increased liver enzyme activities, increased concentrations of TSBA, reduced plasma indocyanine green clearance, and normal total bilirubin concentration [30].

Electroencephalography in dogs with HE reveals a predominance of generalized slow wave activity with increased amplitude [19]. Results of a CSF study from dogs with congenital shunts showed significantly increased levels of glutamate (e.g., 2 to 3-fold increase), glutamine (6-fold increase) and aromatic amino acids (phenylalanine, tyrosine and tryptophan) compared to CSF of control dogs, while concentrations of GABA and branched chain amino acids (valine, leucine,



isoleucine) were within normal limits [58]. It is possible that high concentrations of quinolinic acid and other tryptophan metabolites (e.g., 5-hydroxyindoleacetic acid) in the CNS may contribute to neurologic abnormalities found in dogs with PSS and hepatic encephalopathy [242]. In humans, ammonia metabolites alpha-ketoglutarate and glutamine levels in CSF are elevated and glutamine may be one parameter that is related to the degree of HE [59-61].

Diagnosis of HE may be facilitated by use of radiographic imaging techniques, such as positive contrast portography (considered to be the procedure of choice), computed tomography [62], and transcolonic portal scintigraphy, to demonstrate presence of a small liver and/or anomalous portal vein(s) and large kidneys in dogs with congenital shunts [32,63,64]. Diagnostic gray-scale ultrasonography is another useful technique [65,66]. Experienced surgeons may elect to perform exploratory abdominal surgery. In human medicine, proton magnetic resonance spectroscopy has been used to detect specific metabolic abnormalities (including cerebral increase in glutamine compounds) in the brain (especially in the globus pallidus) in patients with chronic HE [67]. In a recent MRI study in humans with acute HE, cortical lesions resembled those of hypoxic brain damage and were interpreted as acute toxic cortical laminar necrosis [68].

The principal objectives in the specific therapy of HE are listed below.

1. Dietary management. This is aimed at decreasing foods rich in protein, such as meat and egg proteins. Cottage cheese, at 2 g/kg body weight, daily, supplemented with easily digestible carbohydrates (e.g., rice or pasta), can be used to provide most of the caloric needs, along with good quality vitamin (including B vitamins and vitamin A, C, D, E, and K) supplements [28,34]. Note that vitamin K deficiency may develop during liver disease and vitamin K-dependent factors (II, VII, IX, X, and protein C) may be inactivated leading to coagulation abnormalities [56]. Prescription diets (e.g., u/d, k/d; Hill's Pet Products, Topeka, KS) are available to provide protein restricted rations at 1.75 to 2.5 g of protein /kg/day for dogs and 3 to 3.5 g/kg/day for cats [39].
2. Administration of lactulose, a non-absorbable synthetic disaccharide. A recommended dose in dogs is 10 to 40 ml of a 3.35 gm/5 ml solution by gastric tube, three times daily (alternatively, 2.5 to 15 ml for dogs or 1 to 3 ml for cats by mouth, every 8 hours). Dosage can be manipulated so as to produce passage of 2 to 3 soft stools each day. Lactulose results in a marked reduction in the pH of the colonic contents. This, in turn, significantly reduces the formation and absorption of ammonia and other nitrogenous toxins into the portal circulation. Also, the pH gradient causes movement of ammonia into the colon. Dietary supplementation with soluble fiber (psyllium) at 1 - 3 teaspoons daily may also be beneficial [32]. Sodium benzoate is reported to be a safe, cheaper, and effective alternative to lactulose in the treatment of acute portosystemic HE in humans [69].
3. Removal of toxic agents, e.g., bowel cleansing using enemas and/or cathartics; and intestinal antibiotics such as neomycin (20 mg/kg PO bid or tid) or metronidazole (8 mg/kg PO bid). The antibiotics kill colonic bacteria and thereby reduce levels of bacterial nitrogen content and the synthesis of urea.
4. Supportive therapy, e.g., maintaining fluid, electrolyte and acid-base balance).
5. Prevention/control of precipitating factors such as ammonia-producing processes such as GI bleeding (e.g., administration of H<sub>2</sub> receptor antagonists), constipation, and azotemia. In humans with portosystemic encephalopathy, other precipitants include infection, hypokalemia, hypoglycemia, hypoxia, and certain medications (e.g., sedatives and analgesics) [1].

Surgical closure of a portosystemic shunt helps to reverse hepatic atrophy, results in an increased hepatic mass, and corrects imbalances in carbohydrate, lipid, and protein metabolism that are not affected by medical management [70]. Today, total surgical ligation of a single portosystemic shunt is the preferred method of choice [32], although partial ligation/surgical attenuation may be indicated in many cases because of the risk of portal hypertension [71,72], which is characterized by abdominal distension and pain, bloody diarrhea, ileus, endotoxic shock, and peracute cardiovascular collapse [32]. For treatment of single, extrahepatic, portosystemic shunts, this complication may be overcome by gradual vascular occlusion (over 30 to 60 days) using a specialized ameroid constrictor device [73]. Alternatively, the use of transvenous coil embolization and cellophane banding for gradual occlusion of intrahepatic and extrahepatic shunts have been described [74,75]. Use of a portocaval venograft and ameroid ring for the occlusion of intrahepatic portocaval shunts in dogs also shows promising short-term results [76]. Note that following surgical correction of shunts, TSBA levels may not return to normal, even in clinically normal dogs [77]. Transcolonic portal scintigraphy, as well as ultrasound-guided injection of (99M)Tc-macroaggregates into a splenic vein, have been used to evaluate immediate and long-term changes in shunt blood flow after partial ligation of single extrahepatic portosystemic shunts [78,79]. If shunting persists, complete surgical ligation or ameroid constrictor placement is indicated [32].

The prognosis for animals with HE is guarded; however, successful long-term medical and surgical treatment have been reported in young and old dogs with portosystemic shunts [34,37,80,81]. In one study, the outcome of surgical management of intrahepatic portosystemic shunts in dogs was graded as excellent in 75% and grave in 25% [33]. In contrast, a recent study reported that animals with intrahepatic shunts had a significantly lower probability of survival than animals with extrahepatic portocaval or portoazygos shunts [72]. Prognosis appears to be better in dogs with complete surgical ligation [82,83]. Seizures, including status epilepticus, may occur in dogs, especially in older dogs (e.g., >18 months of age) following ligation of portosystemic shunts [84,85,241]. The recommended antiepileptic drug therapy for these dogs is potassium bromide at 100 mg/kg PO qid for 24 hours, followed by maintenance therapy at 30 mg/kg daily [86]. Benzodiazepine therapy should be avoided. Another complication following ligation, usually with a grave prognosis, is portal vein thrombosis [87]. Acute pancreatitis, cardiac arrhythmias, hemorrhage, pulmonary edema, fever and positive blood cultures, as well as intraoperative hypothermia and hypoglycemia are other perioperative complications [33,88,89]. Coagulopathies (including disseminated intravascular coagulation, which can be related to release of thromboplastin and defective clearance of activated clotting factors by the liver) can also be a complication of hepatic necrosis [90].

Primary congenital portosystemic shunts are also an important cause of HE in cats [91,92] and the majority are single extrahepatic shunts [32,93]. Most cats are of mixed breeding, although Persians and Himalayans may be at risk. In contrast to dogs, affected cats present with intermittent clinical and neurological signs, e.g., stunted growth, seizures, ataxia, visual disturbance, tremors or twitching, pupillary dilatation, and behavioral changes, usually accompanied or preceded by ptyalism. Other signs including poor condition, diarrhea, ascites, and polydipsia/polyuria are uncommon [32]. Many affected cats have golden or copper-colored irises [36]. Clinical signs are often first noted in kittens around 10 to 12 weeks of age; however, signs may be first seen in well grown, adult cats. Note that portosystemic shunts can occur in cats without signs of HE but with a history of vague gastrointestinal signs [94]. In one survey of 52 cats with congenital shunts, common biochemical findings were hyperammonemia, increased BSP retention, and high fasting and postprandial TSBA concentrations [95]. In contrast to dogs, only a small percentage of cats have ammonium biurate crystalluria. There appears to be no advantage in performing an ammonium chloride tolerance test in cats that have unequivocal fasting hyperammonemia [96,97]. Surgery appears to be the treatment of choice, and prognosis may be favorable, providing recanalization of the shunt does not occur [96-98], although the outcome of surgical ligation of portosystemic shunts in cats is considered to be less favorable than in dogs [99,100]. Neurological dysfunction occurred in one cat following attenuation of an intrahepatic portosystemic shunt [241]. In a report of per rectal portal scintigraphy in cats, it was concluded that this imaging technique was useful in the diagnosis of congenital portosystemic shunts, facilitated a quantitative assessment of the effects of surgical ligation of the shunting vessel, and might be a more accurate indicator of the degree of shunting after surgery than blood ammonia and TSBA levels [63].

### Hypernatremia

Sodium (Na) is the major extracellular ion (osmole) in the body, including the CNS. Blood sodium levels reflect the ratio of Na to water in the extracellular fluid and account for most of the osmotically active particles in serum. Serum osmolality is defined as the concentration of a solution expressed in osmoles of solute particles per kilogram of solvent. Serum osmolality (normally 290 - 310 mOsm/L) can be calculated by the following formula [101]:

$$2 \times ([Na] + [K]) + \text{glucose}/18 + \text{BUN}/2.8$$

Hypernatremia occurs when serum Na levels exceed the normal range (>156 mEq/L in dogs and >161 mEq/L in cats) [101,102]. It is indicative of a relative increase in total body Na relative to total body water. Causes of hypernatremia include [101-107]:

- Excess water loss, e.g., diabetes insipidus (central or nephrogenic), burns, fever, osmotic diuresis (acute/chronic renal failure, diabetes mellitus, diuretics, or IV solute administration such as mannitol, glucose or urea), osmotic diarrhea (lactulose therapy, malabsorption syndromes, infectious enteritides) and hot weather.
- Excess salt intake, e.g., salt poisoning [107], administration of IV hypertonic solutions (NaCl), sodium bicarbonate, or saline emetics. Water loss and salt gain may occur with hyperaldosteronism and hyperadrenocorticism.
- Insufficient water intake, e.g., lack of access, inability to drink (mechanical inability to prehend or swallow is a potentially serious complication of hypertrophic feline muscular dystrophy), or CNS disease resulting in primary adipsia (absence of thirst), or mental depression, or congenital adipsia. Essential hypernatremia due to failure of the hypothalamic osmoreceptors to respond appropriately to an increase in serum osmolality is rare in small animals

[101]. Note that in normal animals stimulation of thirst and antidiuretic hormone (ADH) release by increasing serum osmolality is the physiologic protection against development of hypernatremia and hyperosmolality. The ADH results in increased renal water reabsorption and increase in urine osmolality.

As with hyponatremia, hypernatremia may be further classified into hypovolemic, normovolemic, and hypervolemic forms [7]. Hypernatremia represents hyperosmolality, and as a consequence, an osmotic gradient is created that results in water movement out of cells into the extracellular fluid. Mild to moderate hypernatremia usually causes minimal clinical signs; however, marked hypernatremia may induce cerebral signs, such as depression, weakness, irritability, uncharacteristic aggression, confusion, propulsive circling, dementia, seizures, coma, and death in dogs and cats as a result of cellular dehydration of neurons [102,106]. Additionally, in people and in experimental animals, shrinkage of brain tissue may cause tearing of vessels, leading to intracranial hemorrhage (e.g., subarachnoid, subdural, intraparenchymal), infarction, venous thrombi, and cerebral edema [108-110]. Neurological signs might not occur until serum Na levels exceed 170 - 175 mEq/l (>350 mOsm/kg) [101,103]. The effects of rising serum osmolality on the nervous system was demonstrated in experimental studies (rabbits) in which predictable signs occurred: lip licking, restlessness, and heightened response to touch were noted with serum osmolality between 350 - 375 mOsm/kg; nystagmus, ataxia, and trunk/limb trembling appeared when osmolalities were in the 375 - 400 range; and finally, when osmolality exceeded 400 mOsm/kg, synchronous/asynchronous jerking movements, limb spasm, reduced responsiveness and death occurred [111]. The severity of the neurological signs is not only dependent on the degree of hyperosmolality but especially on its rate of increase, with signs being most severe in animals with rapidly developing hyperosmolality [102,105]. If the serum is chronically hyperosmolar, the brain compensates by increasing intracellular osmolality by movement of Na, potassium, chloride, and glucose into cells and by production of solutes called osmolytes or idiogenic osmoles (these include amino acids such as glutamine, glutamate, aspartate, creatine, and taurine, as well as myo-inositol and glycerophosphoryl-choline) which help normalize brain water content [112-115].

Pathological studies of brain lesions associated with hypernatremia are somewhat sparse. In one case involving hypernatremia and adipsia in a 4.5 month old female Dalmatian puppy with diabetes insipidus associated with inadequate ADH secretion, a nuclear scan of the cranial vault was normal, as were skull radiographs and CSF analysis [106]. Pathological studies revealed extensive dysplastic malformation involving midline structures of the frontal lobes and rostral diencephalon. These included absence/reduction of the corpus callosum at rostral/caudal levels, frontal lobe fusion in the median plane ventrally including caudate nuclei and prorean gyri (both of which blended caudally with the rostral hypothalamus), and absence of rostral part of the fornix, its columns, septum pellucidum, and septal nuclei. The pituitary gland was normal. The dysplasia was considered to involve the nuclei normally related to thirst regulation and ADH formation. In a 7 month old female Miniature Schnauzer with seizures, hypernatremia and adipsia associated with defective osmoreceptor function, suggesting this was a case of essential hypernatremia (the dog did not have diabetes insipidus), astrogliosis and neuronal degeneration were detected in thalamic and hypothalamic regions but were considered to be nonspecific lesions related to the seizures [116]. The authors of this report added an addendum that they had seen two additional young female Miniature Schnauzers with thirst deficiency and neurological signs associated with hypernatremia. In one of these dogs necropsied, no pathological changes were found in the thalamic/hypothalamic region. In a further canine case characterized by seizures and hypodipsic hypernatremia associated with defective osmoregulation of ADH, pathological changes including hydrocephalus, atrophy of the septum pellucidum, and neuroaxonal dystrophy of the cuneate nuclei were observed at necropsy [117]. Pressure atrophy of osmoreceptors in the hypothalamus secondary to hydrocephalus was postulated. The underlying cause of the pathological changes was not determined. Adipsia/hypernatremia in a 7 year old Doberman was thought to be the result of destruction of hypothalamic osmoreceptors by a focal granulomatous meningoencephalitis [250]. In a report of a fatal hypernatremia from salt ingestion in a 8 year old male Airedale Terrier, CNS lesions included intracranial hemorrhage, thrombosis, and vascular stasis with engorgement of vessels, along with diffuse white matter vacuolation [107]. The authors considered that the cerebral edema might have followed prolonged seizure activity or was due to isotonic water intoxication (Plasma-Lyte was administered initially followed by 5% dextrose solution).

For treatment, a solution of 5% dextrose can be administered intravenously for acute hypernatremia [12]; however, oral administration of fluids is recommended for treating chronic hypernatremia since rapid correction may lead to cerebral edema (water intoxication), seizures, and death because of the accumulated intracellular idiogenic osmoles [105,118] (see also the pathophysiology associated with too-rapid correction of hyponatremia). A caveat is that excessive ingestion of water mixed with food may result in hyponatremia and neurological deterioration associated with cerebral edema [238]. The water deficit may be calculated [12,105] using the following formula:

$$\text{Water deficit (L)} = 0.6 \times \text{lean body weight (kg)} \times (\text{patient's Na/normal Na} - 1)$$

For animals with acute-onset symptomatic hypernatremia, a decline of serum Na around 1 mEq/L per hour can be safely performed; however the rate of decline in animals with chronic hypernatremia should not exceed 0.5 mEq/L per hour [101]. Of course, therapy for hypernatremia should also be directed at the underlying cause. Prognosis for acute hypernatremia is guarded. Adipsic animals may be maintained for several years by combining water with food [106,116,238]. Diuretics (e.g., furosemide) are recommended for animals with hypernatremia caused by excessive salt intake to prevent development of pulmonary edema during fluid therapy [103,107].

**Hypernatremic Myopathy** - Episodic weakness and signs of depression were reported in a 7 month old Domestic Shorthaired cat with episodic hypernatremia (serum Na concentration ranging from 182 to 215 mEq/L; normal is 148 to 161 mEq/L) secondary to hypodipsia (failure to drink water) [119]. This rare condition was accompanied by hyperosmolality (ranging from 381 to 431 mOsm/L) and evidence of hypopituitarism (adrenocorticotrophic and growth hormone deficiencies, along with blunted thyroxine response to thyroid-stimulating hormone). The most prominent clinical sign was ventral flexion of the neck. No other neurological abnormalities were detected. Electromyographic testing revealed prolonged insertional activity, fibrillation potentials, positive sharp waves, and bizarre high-frequency discharges. Nerve conduction velocities were normal. These abnormalities were more severe during episodes of hypernatremia. Serum creatine kinase activity was increased, while CSF analysis was normal. Examination of several muscle biopsies were normal. Contrast-enhanced computed tomographic studies of the brain demonstrated marked hydrocephalus, although no hypothalamic or pituitary lesions were detected. The episodic weakness might have been associated with muscle membrane alterations associated with displacement of intracellular potassium by high levels of extracellular sodium. Interestingly, the clinical signs, serum CK levels, electrodiagnostic data, and muscle biopsy findings were very similar to those seen in cats with hypokalemic myopathy. Forced water intake and dietary sodium restriction (using a low-salt feline diet) corrected the hypernatremia and signs of muscle dysfunction. After restoration of eunatremia, secretion of pituitary hormones became normal. It was suggested that hypothalamic dysfunction, possibly related to hydrocephalus, induced both hypodipsia and transient hypopituitarism [119].

### **Hypocalcemia**

Ionized calcium is important for presynaptic neurotransmitter release from synaptic vesicles and stabilization of nerve and muscle membranes [1]. As a result of reduction in extracellular fluid concentration of calcium ions, and since divalent cations have a stabilizing effect on nerve and muscle membranes [120], the nervous system becomes increasingly excitable due to increased neuronal membrane permeability to sodium. Nerve fibers discharge spontaneously resulting in skeletal muscle contraction and tetany.

Total serum calcium is approximately 50% ionized, 40% protein bound (especially to albumin), and 10% complexed with anions such as citrate or phosphate [121]. Only ionized calcium is biologically active in bone formation, neuromuscular activity, blood coagulation, and cellular biochemical processes. The proportion of ionized calcium is affected by acid-base balance: ionized calcium levels are decreased by alkalosis and increased by acidosis. Total serum calcium and protein-bound calcium are decreased in hypoproteinemia, but ionized calcium levels remain normal. Accordingly, clinical signs of hypocalcemia do not occur in hypoalbuminemic conditions. The correction formula based on serum albumin concentration is [122]:

$$\text{Corrected total calcium level (mg/dl)} = \text{measured calcium (mg/dl)} - \text{albumin (g/dl)} + 3.5$$

(Note that assessment of ionized calcium levels are preferable to such formulas and today are readily available in commercial laboratories and are inexpensive).

Serum calcium levels usually represent a balance between bone formation and bone resorption which is regulated by parathyroid hormone (PTH), 1,25-dihydroxycholecalciferol, and calcitonin. Except for acid-base imbalance and hypoalbuminemia, hypocalcemia usually indicates hormonal imbalance [121]. Dietary intake of calcium rarely affects serum levels directly.

Hypocalcemia may be seen with:

1. Hypoparathyroidism. In normal animals, an inverse linear relationship exists between parathyroid hormone (PTH) and serum calcium levels, e.g., a fall of serum calcium levels below 10.5 mg/dl stimulates PTH secretion, while calcium levels > 10.5 mg/dl result in suppression of PTH secretion [122]. With hypoparathyroidism, there is a decrease in serum calcium concentration and an increase in plasma phosphate levels (associated with loss of PTH actions on mobilizing calcium and phosphate from bone and retention of calcium and enhancing phosphate secretion by the kidneys). Primary hypoparathyroidism results from absolute or relative deficiency of parathormone and is infrequently seen in dogs and cats [123-131]. Hypocalcemia has also been seen with secondary hypoparathyroidism attributable to hypomagnesemia [243]. Animals have been classified as having 'idiopathic hypoparathyroidism' in the absence of trauma, malignant or surgical destruction, or other obvious damage to the neck or parathyroid glands [122,132,133]. The histological interpretation is lymphocytic parathyroiditis since the glands are microscopically atrophied with infiltration/replacement by lymphocytes, plasma cells, fibrous connective tissue and capillary proliferation. Commonly reported canine breeds include Poodles, Miniature Schnauzers, Retrievers, German Shepherds and Terriers [122].
2. Nutritional hyperparathyroidism (typically a disease of young growing animals) occurs secondary to dietary calcium deficiency, hypovitaminosis D, or dietary phosphate excess. This is an uncommon condition, especially in cats, due to the wide availability of commercial balanced diets, that usually results from animals fed foods such as beef heart or liver that have low calcium-to-phosphorus ratios (note that all-meat diets are extremely low in calcium and have a low phosphorus concentration resulting in a low calcium:phosphorus ratio [134]). In an attempt to maintain mineral homeostasis, the low dietary calcium results in a transient decrease in serum calcium, inducing increased PTH release which leads to accelerated bone resorption and reduction in bone mass as calcium is removed from bone, increased renal calcium reabsorption and phosphorus excretion, increased renal synthesis of active vitamin D (calcitriol), and eventually the development of skeletal disorders including osteopenia (marked decrease in bone opacity), vertebral lordosis/kyphosis, bone pain, and pathologic fractures, including the vertebrae. Note that affected animals usually have normal serum levels of calcium and phosphorus [122], although in one recent report, 4 of 6 affected young cats were hypocalcemic [134]. In this study, serum PTH levels were markedly elevated, 1,25(OH)<sub>2</sub>-vitamin D<sub>3</sub> (calcitriol) levels were mildly increased, while 25(OH)-vitamin D<sub>3</sub> concentration was mildly decreased [134].
3. Renal disease (acute and chronic) - associated with decreased renal hydroxylation of vitamin D, soft-tissue calcification, reciprocal decrease in calcium serum levels secondary to hyperphosphatemia, and skeletal resistance to the effects of parathormone [121]. Note that uremic acidosis results in an increased proportion of ionized calcium in serum that may prevent signs of tetany in a hypocalcemic animal [122].
4. Acute pancreatitis in which ionized calcium may be bound to free fatty acids in necrotic fat [121,122,135]. The hypocalcemia is usually mild and subclinical in dogs with pancreatitis and any co-existing acidosis (frequently present in acute pancreatitis) will increase the levels of ionized calcium [122].
5. Post-parturient eclampsia (most common in small dogs; less common in cats and large dogs) [121,122,136].
6. Ethylene glycol toxicity in dogs and cats [122,137].
7. Intestinal malabsorption in dogs [121,122].
8. Commercial phosphate-containing enemas (resulting from acute, severe hyperphosphatemia following colonic absorption of the enema solution) [138].
9. Miscellaneous causes include trauma to the parathyroid glands, thyroid medullary carcinoma, various primary and metastatic bone tumors, and some forms of chemotherapy [122]. There has been a report of acute hypocalcemia in 2 dogs associated with infarction of parathyroid gland adenomas that were previously responsible for causing persistent hypercalcemia. [139]. In experimental studies in which gnotobiotic dogs were infected by canine distemper virus, some infected dogs had low serum calcium concentrations associated with ultrastructural evidence of parathyroid gland inactivity, degeneration, and viral inclusions [140]. Hypocalcemia has also been seen following administration of sodium bicarbonate for salicylate intoxication in a cat [141].

In dogs and cats, hypocalcemic tetany may occur when serum calcium levels are less than 6 mg/dl, or when ionized calcium levels are less than 2.5 mg/dl [121]. Clinical signs of hypocalcemia are characterized by abrupt onset of intermittent neurological or neuromuscular disturbances. Signs include nervousness, panting, pacing, muscle spasm and cramping, often seen in leg muscles, focal muscle twitching, trembling, stiff-stilted gait, intense facial rubbing with the paws or on the ground, ataxia, tonic-clonic spasms, episodic rigidity and falling, tetraparesis, and sometimes seizures and status epilepticus. In a recent report on nutritional secondary hyperparathyroidism, 4 of 6 cats were presented for evaluation and treatment of seizures (3 of these cats were hypocalcemic) [134]. Hypocalcemic animals are frequently febrile. Nictitating membranes may be raised in cats. Some animals manifest mental dullness and appear disoriented. Typical electrocardiographic findings include deep, wide T waves, prolonged Q-T intervals, and bradycardia [122]. Diagnosis of hypocalcemia is based on clinical

signs and serum ionized calcium levels.

Hypocalcemic tetany requires prompt and immediate replacement of calcium, e.g., calcium gluconate as a 10% solution at 1 - 1.5 ml/kg or 5 - 15 mg/kg, IV, slowly over a 10 to 30 minute period [122]. Following control of the tetany, the same dose can be given subcutaneously (diluted in an equal volume of saline) every 6 to 8 hours while waiting for oral vitamin D and calcium supplementation to take effect (this usually requires a period of 24 to 96 hours). Once serum calcium levels are stable, the subcutaneous injections can be gradually tapered (serum calcium levels should be maintained above 8 mg/dl). Oral calcium supplements should be given to animals initially with primary hypoparathyroidism, e.g., calcium carbonate tablets at 0.5 - 1 g/day (cats) and 1 - 4 g/day (dogs) in divided doses, for several weeks or months, according to serum calcium levels. After this period calcium in balanced diets is usually sufficient. Vitamin D therapy, however, is usually permanent for animals with primary hypoparathyroidism. Vitamin D increases serum calcium by promoting intestinal absorption.

Suggested dosages are [122]:

- Vitamin D2 (ergocalciferol) at 4000 - 6000 U/kg/day initially for several weeks, followed by a maintenance dose of 1000 - 2000 U/kg once daily to once weekly, depending on monitored serum calcium levels; or
- Dihydrotachysterol at 0.02 - 0.03 mg/kg/day initially for several weeks, followed by a maintenance dose of 0.01 - 0.02 mg/kg q24 - 48h. This preparation raises serum calcium levels faster than vitamin D2 and its effects dissipate quicker once administration is stopped.

Treatment of animals with nutritional secondary hyperparathyroidism entails short- term parenteral calcium gluconate injections as clinically indicated, a balanced diet, and cage rest [122,134].

Prognosis will depend upon the underlying cause of the hypocalcemia. Correct dosage and owner compliance may result in excellent prognosis for animals with uncomplicated primary hypoparathyroidism; however, animals with spinal fractures have a guarded prognosis [134]. Note that uncontrolled motor activity as a result of seizures and/or excessive muscle jerking in animals with vertebral osteopenia will place these animals at high risk for spinal cord damage secondary to spinal fracture [134]. Iatrogenic hypoparathyroidism in cats resulting from neck surgery is often transient and lifelong treatment is not always necessary [122]. The prognosis for uncomplicated cases of nutritional secondary hyperparathyroidism is good [134].

### **Hypoglycemia**

Glucose is the major nutritive carbohydrate substrate of the brain which requires about 100g glucose/day for normal functions [1,86]. This dependence on glucose, along with the brain's limited glycogen stores, results in rapid CNS dysfunction when hypoglycemia is present and permanent neurological sequela if the condition is prolonged [1]. Counterregulatory (i.e. glucose-raising) hormones (in particular, epinephrine and glucagon, but also norepinephrine, growth hormone, and cortisol) are released once blood glucose reach critical levels, e.g., < 40 mg/dl with induction of gluconeogenesis [142-144]. If the glucose levels decline slowly, the CNS is able to utilize alternative non-glucose organic substrates, such as ketoacids, intermediaries of glucose metabolism, and certain amino acids [1,145,146]. In people, neuronal damage consecutive to severe and prolonged hypoglycemia occurs mainly in the cerebral cortex, hippocampus and caudate-putamen as a result of active extracellular release of excitatory amino acids [147-149]. Neuropathological studies have been limited in dogs, although early signs of acute neuronal necrosis were reported exclusively in the superficial layers of the cerebral cortex, in addition to spongy changes in the dentate gyrus of the hippocampus in a 5 year old female Collie dog with hypoglycemia [150]. In another dog, there was extensive bilateral polioencephalomalacia observed in the cerebral cortex and basal nuclei [151]. Hypoglycemic Toy-breed puppies with hepatic steatosis (fatty liver) have ischemic neuronal changes in the cerebral neocortex [152]. The apparent selective vulnerability of certain neurons to hypoglycemia mimics that seen in hypoxic-ischemic conditions (e.g., cardiac arrest) and seizures [153]. Curiously, it has been reported that cats appear to have high resistance to brain injury caused by hypoglycemia [154]. Hypoglycemia plus hypoxia has been equated with tissue ischemia [40].

A common cause of hypoglycemia in dogs is a functional islet cell tumor (synonyms are hyperinsulinism, beta cell tumor, and insulinoma) [155]. These tumors occur in middle-aged to older dogs, of either gender, and are associated with increased insulin or proinsulin secretion by functional, neoplastic beta cells ("islet" cells) of the pancreas, independent of the negative feedback effects caused by hypoglycemia [156-160]. While a wide variety of breeds may be affected, Labrador Retriever, German Shepherds, Irish Setters, Standard Poodles, Collies, Boxers, and Fox Terriers may have a higher incidence than other breeds. Insulinomas occur less frequently in cats [161-164]. Clinical signs of hypoglycemia may reflect both neuroglycopenia (generalized seizures, weakness, ataxia, collapse, lethargy, transient blindness, and abnormal behavior, e.g., hysteria) and sympathoadrenal stimulation (muscle tremors, nervousness, restlessness, and hunger) [6]. The adrenergic signs precede neurobehavioral signs in humans and thus function as an early warning system [165]. Signs are often intermittent initially but become more frequent as the disease progresses. There is a strong correlation between onset of

clinical signs of hypoglycemia and fasting, excitement, exercise, or eating [6,166]. Food consumption may stimulate excessive insulin secretion by the tumor resulting in postprandial hypoglycemia 2 to 6 hours later [6]. Polyneuropathy may be another complication of insulinoma in dogs [157,167-173]. Clinical signs range from paraparesis to tetraplegia, facial paresis/paralysis, hyporeflexia, hypotonia, and muscle atrophy, usually in conjunction with seizures, etc. Histopathological findings in nerves from affected dogs include severe axonal necrosis, nerve fiber loss, and variable demyelination. Muscle changes reflect neurogenic atrophy.

Results of CBC and urinalysis are usually normal. Hypoglycemia is the only consistent abnormality identified in serum biochemical profiles in animals with insulin-secreting tumors [6]. In one study involving 71 dogs with insulinomas, the mean initial blood glucose concentration was 46 mg/dl [6]. A serum insulin concentration  $> 20 \mu\text{U/ml}$  in a dog with a blood glucose level  $< 60 \text{ mg/dl}$  is strong evidence for the diagnosis of an insulinoma. Some dogs may be euglycemic, necessitating hourly evaluations of blood glucose concentrations during a 4- to 12-hour fast. In one study, a fast of 8 hours was successful in demonstrating hypoglycemia in 26 of 28 trials in 25 dogs with insulinomas [174]. Some researchers no longer recommend use of insulin:glucose ratios because of false-negative and false-positive results [6,175,176]. Abdominal radiographic studies are usually normal. Since tumor metastasis to the lungs is extremely rare [6], thoracic radiographs are of limited help in evaluating metastatic disease. Abdominal ultrasonography may sometimes identify a pancreatic, peripancreatic, or hepatic mass [6,177]. Ultrasound may also detect biliary obstruction caused by the tumor [177]. Scintigraphy has been used to identify tumors and metastases (often to liver and mesenteric lymph node) in dogs [178,179]. In one report, somatostatin receptor scintigraphy using indium In-111 pentetreotide was performed [178].

Definitive diagnosis is obtained by surgical exploration, biopsy and histopathological examination of the tumor. Insulin-secreting tumors can often be visualized or palpated by the surgeon [6]. As islet cell tumors in dogs and cats are frequently malignant with metastasis occurring early in the course of the disease, usually to regional lymphatics and lymph nodes (e.g., duodenal, mesenteric, hepatic and splenic nodes), liver, mesentery, and omentum [6], careful inspection of these sites is imperative. Surgical removal is the treatment of choice [6,180]. Immunohistochemical studies of 20 islet cell tumors in dogs revealed that 8 of the 20 tumors had positive immunoreactivity for insulin, 9 for glucagon, 14 for somatostatin, and one for gastrin [159]. Three tumors were pure insulinomas, but no pure somatostatins, glucagonomas, or gastrinomas were identified. Most tumors and metastases had mixed positive immunoreactivity; one neoplastic cell type predominated with lesser numbers of other cell types. The authors noted that the tumor staining pattern did not correlate consistently with function, as determined by blood glucose and serum insulin assays. Positive immunoreactivity has also been shown for insulin, somatostatin, and islet amyloid polypeptide in an islet cell tumor in a cat [162].

With inoperable cases (e.g., animals with extensive local tumor spread or metastatic disease, older animals, or animals that are anesthetic risks) medical therapy for chronic hypoglycemia evolves around frequent feedings of diets high in proteins, fats, and complex carbohydrates, in conjunction with prednisone at 0.25 - 0.5 mg/kg/day, PO, in two divided doses (dogs), and/or diazoxide, from 10 to 60 mg/kg, divided into 2 doses daily (not to exceed 60 mg/kg/day for dogs) [6,181,182]. Prednisone antagonizes the effects of insulin at the cellular level and promotes gluconeogenesis, while diazoxide inhibits the release of insulin, inhibits tissue use of glucose, enhances epinephrine-induced glycogenolysis, and increases the rate of mobilization of free fatty acids. Neither drug has any effect on tumor growth or metastasis. In a dog with an insulinoma-related peripheral polyneuropathy, frequent feeding and treatment with corticosteroids resulted in recovery from a non-ambulatory to an almost completely normal clinical state, despite the persistence of hypoglycemia and hyperinsulinism [183]. Frequent feedings and prednisone (5 mg, sid or bid, PO) have been used in successfully treating a cat with chronic hypoglycemia associated with insulin-secreting pancreatic islet cell carcinoma [163]. Variable results have been obtained with the long-acting somatostatin analogue, octreotide acetate (SMS 201 - 995; Sandostatin®) in dogs with insulinoma [184].

The long-term prognosis for animals with islet cell tumors is guarded to poor. In canine surgical cases, a mean post-operative survival time is reported to be 12 to 14 months [6,174]. In dogs treated only medically, the mean survival times drop to around 90 days, with few dogs surviving a year [6]. One surgically-treated cat survived 7 months [162], while a medically managed cat survived 18 months [163]. Postoperative complications can include acute pancreatitis and diabetes mellitus (which may develop as a result of chronic beta cell suppression by the excessive insulin levels). Sometimes the diabetes persists, necessitating a low-carbohydrate diet and/or insulin administration. Dogs that remain hypoglycemic after surgical removal are considered to have functional metastases [6].

**Miscellaneous Causes of Hypoglycemia** - Hypoglycemia has been reported in association with various non-islet cell tumors in dogs, including hepatocellular carcinoma, hepatoma, hemangiosarcoma, hepatic leiomyosarcoma, splenic hemangiosarcoma, salivary gland adenocarcinoma, metastatic oral melanoma, metastatic mammary carcinoma, primary pulmonary adenocarcinoma, and lymphatic leukemia [185-187]. In the dog, non-islet cell tumor hypoglycemia has been attributed to excess production of IGF-II (insulin-like growth factor II) circulating in a molecular form that can easily cross the capillary wall to exert its insulin-like effects on target tissues [188]. Removal of the tumor can result in return of normal

blood glucose levels and remission of clinical signs [186].

Transient, juvenile hypoglycemia may occur in neonatal puppies and in toy and miniature-breed puppies less than 3 months of age as a result of cold, starvation, or gastrointestinal disease. It may also be seen with liver insufficiency (e.g., portal shunt). These disorders usually respond to a dietary carbohydrate source. Feeding puppies and the bitch with a protein-rich diet reportedly prevented the juvenile hypoglycemia seen in the Yorkshire Terrier breed and other toy breeds [189]. A 50% dextrose solution, at a dose of 0.5 to 1.0 ml/kg administered slowly over 10 minutes, IV, may be given for temporary control of seizures in animals with a hypoglycemic crisis [190]. The cause of transient hypoglycemia is unknown but it may be related to enzyme immaturity leading to depletion of primary energy sources, such as ketones or glucose [191]. Another cause of juvenile hypoglycemia is glycogen storage disease (see glycogenoses).

Hypoglycemia can result from excessive insulin administration to animals with diabetes mellitus [4], and cats may be at greater risk of insulin overdose than dogs, especially if the cats are obese and receiving insulin doses > 6 U/injection, administered once or twice daily [192]. Interestingly, in some affected diabetic dogs and cats, sympathoadrenal signs were either not seen or not recognized [192]. Treatment of such cases includes administration of a slow bolus of 50% dextrose at 0.5 g/kg, diluted 1:4, followed by a continuous infusion of 5% dextrose to maintain normal blood glucose levels, and the animal fed as soon as it is able to eat unassisted [4]. In adult dogs, hypoglycemia may also occur with severe hypoadrenocorticism, liver disease (e.g., impaired glucose production and glycogen storage), sepsis, glycogenoses, and as a complication of pregnancy accompanied by ketonuria [6,193]. Spontaneous hypoglycemia has been reported in a 9 year old cat with chronic renal failure [194]. Hypoglycemia in highly nervous hunting dogs is also well recognized. Attacks are characterized by apparent disorientation, weakness and generalized seizures. Recovery is rapid; however the affected animal's hunting ability is compromised. Frequent feedings with protein-rich foods and/or candy bars may prevent the attacks. The cause has not been determined.

### Hyponatremia

Hyponatremia is a metabolic state in which serum sodium (Na) levels are < 146 mEq/L in dogs and < 151 mEq/L in cats [102]. True hyponatremia is associated with serum hypoosmolality (< 290 mOsm/L) which suggests total body water in excess of Na [1,101]. Hyponatremia generally results from retention of ingested or administered water and usually indicates a defect in renal water excretion (e.g., inappropriate reabsorption of water in proportion to Na, or failure to reabsorb sodium by the kidney) and with urine specific gravity > 1.003 [102]. Electrolyte loss in excess of water may cause hyponatremia but this is uncommon. Hyponatremia with normal or increased serum osmolality is termed *pseudohyponatremia*. Hyperosmolar pseudohyponatremia may be associated with administration of hypertonic mannitol or parenteral hyperglycemia [195], urea nitrogen, or toxins that attract water into the intravascular space and dilute serum Na concentration. Differential diagnosis might include diabetes mellitus, ethylene glycol toxicity, and renal failure [101]. Isoosmolar pseudohyponatremia is often seen with hyperlipidemia and hyperproteinemia [102]. True hypoosmolar hyponatremia can be further subdivided, based on extracellular fluid volume, into [1,102]:

- a. Hypervolemic (e.g., congestive heart failure, liver failure, nephrotic syndrome, hypoalbuminemic states)
- b. Normovolemic (e.g., syndrome of inappropriate antidiuretic hormone secretion, primary polydipsia, water intoxication, hypothyroidism, adrenal insufficiency [196], or renal failure;
- c. Hypovolemic (e.g., renal or extrarenal disease, such as gastrointestinal, third space or cutaneous losses).

Neurological signs of hyponatremia are related to the rapidity of onset of the hyponatremia [12,105]. In acute hyponatremia, water flows down the its concentration gradient and enters brain cells producing cerebral edema and increased intracranial pressure [1]. Signs range from generalized weakness and mental depression to stupor, coma, seizures, and dementia [197]. Treatment is aimed at increasing serum Na levels and treating the underlying cause of the hyponatremia. Administration of hypertonic saline (e.g., 3 - 5%) should be given to animals in which serum Na is < 115 mEq/L. The Na deficit may be calculated using the following formula [101]:

$$\text{Na deficit (mEq/L)} = (140 - \text{measured Na}) \times \text{body weight (kg)} \times 0.3$$

The replacement fluid should be given slowly over 12 to 24 hours. Normal isotonic saline can be given to hypovolemic animals, while water restriction (i.e. limiting water intake to less than urine output) can be performed for animals with normovolemia or hypervolemia associated with excessive water intake or renal retention. In instances where severe neurological signs are seen associated with normal or excessive intravascular fluid, furosemide (at 2 - 4 mg/kg IV) can be used to promote renal water excretion [101].



Treatment of chronic cases of hyponatremia may present a different challenge. Paradoxically, the neurological condition of some patients with severe hyponatremia may actually deteriorate as their electrolytes get better. In hyponatremic people in whom correction of the hyponatremia occurs too rapidly (e.g., correction of hyponatremia by more than 12 mEq/L per day), a demyelinating condition termed central pontine myelinolysis is well recognized in which nerve cells and axons are spared but there is loss of oligodendrocytes [197,198]. This disorder is characterized by symmetrical myelinolytic foci in the pons and sometimes (in approximately 10% of cases) in extrapontine areas such as thalamus, subthalamic nucleus, striatum, internal capsule, amygdaloid nuclei, lateral geniculate body, white matter of cerebellum foliae, and deep layers of the cerebral cortex and adjacent white matter [199]. Results of an immunohistochemical study of central pontine myelinolysis in people indicated reduced immunoreactivity of myelin basic protein, myelin-associated glycoprotein, transferrin, and carbonic anhydrase C, and dystrophic astrocytic alterations based on labeling of glial fibrillary acidic protein and S-100 protein [200]. The exact pathogenesis of this myelinolysis still has not been determined but it certainly appears to be associated with the electrolyte derangement [201]. One hypothesis is that chronic hyponatremia (e.g., 2 - 3 days) may allow the brain to compensate for the imbalance in the osmotic gradient by active extrusion of intracellular electrolytes (sodium, potassium, and chloride) followed by organic osmolytes ("idiogenic osmoles"), including amino acids glutamine, glutamate and taurine, as well as myoinositol, phosphocreatine/creatine, and glycerophosphorylcholine [114,202], and thereby reduce the brain edema. Although the adaptive solute loss from the brain helps protect against cerebral edema in severe hyponatremia, it also places the brain at risk to dehydration when serum sodium levels are returned to normal, since with rapid correction of chronic hyponatremia, compensatory influx of electrolytes is not matched by the slower moving organic osmolytes as serum becomes hypertonic relative to the CNS [203]. This sudden new osmotic gradient can lead to cellular dehydration, including possible axonal shrinkage away from myelin sheaths and other events leading to subsequent demyelination [203]. Results of an experimental study indicated that following rapid correction of chronic hyponatremia, a topographic correlation occurred between demyelination lesions and delayed accumulation of organic osmolytes [204]. There have been a few reports of a similar pathophysiological event occurring in dogs following rapid correction of naturally occurring hyponatremia using 0.9% saline (the rate of correction in two dogs ranged from 16 to 22 mEq/L/day, while in the third dog, the rate was 17mEq/L in 9 hours) [205,206]. Interestingly, the cause of the hyponatremia was heavy whipworm (*Trichuris vulpis*) infestation in all cases. Neurological signs were seen several days after saline infusion and included ataxia, weakness, hypermetria, visual deficits, depressed menace responses with normal pupillary light reflexes, deficient postural reactions, trismus, exaggerated licking movements, episodic myoclonus, episodic whole-body spasms, obtundation and tetraparesis. In experimentally induced hyponatremia in dogs, several were stuporous or comatose [197]. Cerebrospinal fluid evaluation in two clinically-affected dogs tested was normal. T2-weighted magnetic resonance imaging in two clinically-affected dogs revealed symmetrically increased signal intensity in the area of the central thalamic nuclei, which in one dog progressed to a marked increase in signal intensity with ring-like effects [205]. In one dog necropsied, macroscopic tan-colored foci were seen in the central lateral thalamus bilaterally (the more prominent being approximately 4x5x3 mm in size). Microscopic lesions were found in the thalamus as well as in the rostral commissures. Lesions were characterized by myelin loss, apparent decrease in numbers of oligodendrocytes and increased numbers of astrocytes, and degenerating oligodendrocytes, some of which appeared to have pyknotic nuclei and vacuolated cytoplasm. Axons and nerve cell bodies appeared normal. Myelin splitting was observed intrastructurally, and cells considered to be oligodendrocytes had electron-lucent cytoplasm containing numerous, dilated membrane-bound vacuoles. The authors stated that the myelin loss appeared to be secondary to acute degeneration and probable loss of oligodendrocytes and other glia [205]. In experimental studies using dogs in which hyponatremia was rapidly corrected using 3% saline (at a correction rate of 15 mEq/L/day), symmetrical lesions primarily involving myelin and oligodendrocytes were seen in the thalamus and other areas including the central pons, lateral aspects of the thalamus and adjacent internal capsules, caudate nucleus, putamen, red nuclei, deep layers of cerebral cortex and subjacent white matter, and cerebellum [197]. The histological lesions were almost identical to the naturally occurring lesions, although some loss of axons and neurons were found at the center of the lesions. Also, Purkinje cells loss was noted in areas of severe white matter involvement, and fibrillary gliosis was present in chronic lesions [197]. The cause(s) of this regional vulnerability in animals and people remains undetermined. The prognosis of dogs with hyponatremia-related myelinolysis is guarded to favorable. While one affected dog was euthanized, two others slowly recovered completely without medication over the ensuing 4 - 7 weeks [205,206]. In summary, in order to avoid rapid normalization of severe, sustained hyponatremia, recommended rates of correction for animals with chronic hyponatremia are 10 - 12 mEq/L per day or approximately 0.5 mEq/L per hour [205,206].

### **Hypothyroidism**

Hypothyroidism results from decreased production of thyroxine (T4) and triiodothyronine (T3) by the thyroid gland. Thyroid hormones have myriad functions, for example, they increase metabolic rate and oxygen consumption of most tissues, have positive inotropic and chronotropic cardiac effects, increase the number/affinity of beta-adrenergic receptors, enhance response to catecholamines, have catabolic effects on muscle and adipose tissue, stimulate erythropoiesis, regulate

cholesterol synthesis/degradation, and are essential for normal development of nervous and skeletal systems [207]. Hypothyroidism is common in dogs but rare in cats and most cases of acquired canine hypothyroidism are associated with immune-mediated lymphocytic thyroiditis/idiopathic thyroid atrophy [208,209]. An association between hypothyroidism and acquired myasthenia gravis has been suggested in dogs [239]. A recent study of a closed colony of Beagles showed that dogs with hypothyroidism associated with lymphocytic thyroiditis had an increased risk for thyroid follicular epithelial neoplasia [210]. Hypothyroidism is more common in certain breeds, such as Doberman Pinscher and Golden Retrievers, especially in neutered animals [211]. Common clinical findings include obesity, seborrhea, alopecia, weakness, lethargy, bradycardia, and pyoderma [211]. Impaired ventricular function, along with decreased amplitude of the P and R waves, has been shown in echocardiographic and electrocardiographic studies [212]. Clinicopathologic abnormalities may include hypercholesterolemia, non-regenerative anemia, high serum alkaline phosphatase activity, and high serum creatine kinase activity [207,211].

Myxedema coma is an extremely rare form of decompensated hypothyroidism [213] in which patients may manifest bradycardia, hypothermia, and stupor/coma, along with hypoventilation, hypoxia, and hypotension [214-216]. The hypothermia in affected dogs tends to be characterized by absence of shivering [214,217]. The pathogenesis of the coma remains enigmatic [1], although it has been stated that the hypothyroidism is often profound and associated with an inciting event such as respiratory depressant drugs, infectious diseases (especially respiratory), heart failure, decreased blood volume (e.g., diuretics), or other stressors such as exposure to cold environment or surgery [1,217,218]. In affected dogs, the more classical signs of hypothyroidism (see above) will also be present [217].

Diagnosis of hypothyroidism is suggested by low resting free T4 levels and confirmed by performing a thyroid stimulating hormone (TSH) response test. A diagnosis is likely if both the pre- and post-TSH serum total T4 levels < 1.5 µg/dl [207]. Treatment involves administration of synthetic L-thyroxine at 0.02 mg/kg PO, bid for several weeks, according to results of therapeutic monitoring. Maintenance dosage is at 0.02 mg/kg PO daily, once clinical signs have resolved and total T4 levels are normalized [207]. Recommended dosage of L-thyroxine for animals in myxedema coma is 5 µg/kg every 12 hours, intravenously, along with fluid therapy, warming and ventilatory support [207]. Administration of glucocorticosteroids and broad-spectrum antibiotics has also been suggested [217]. If possible, the diagnosis of myxedema coma should be suspected based on the clinical presentation, and treatment should not be delayed while awaiting confirmatory laboratory data [217]. Prognosis is guarded for animals with myxedema coma. In a recent report involving a 7 year old male English Coonhound with suspected myxedema coma (the dog was comatose and cold to the touch, had bilateral rotary nystagmus, bradycardia and irregular cardiac rhythm, a non-detectable peripheral pulse, and showed bilaterally symmetrical alopecia of the base of the ears and caudal aspects of the thighs) [216], successful treatment involved a combination of active external and core rewarming techniques (e.g., recirculating water heating pads placed over and under the dog), intravenous (1.0 µg/kg, q 12h) and oral (4.0 µg/kg, q 12h) administration of L-thyroxine, supplemental oxygen, and administration of warmed fluids (Lactated Ringer's solution and 0.9% saline at 20 ml/kg).

Signs of CNS disease may also occur in dogs with hypothyroidism and atherosclerosis (see infarction), while secondary hypothyroidism can be caused by pituitary tumors (see neoplasia). Signs of peripheral nerve disease are commonly encountered in animals with hypothyroid neuropathy.

### **Uremic Encephalopathy**

Uremic encephalopathy (UE) is an ill-defined condition that has been infrequently reported in young and old dogs with renal failure [40,219,220]. Clinical signs include depression or stupor, generalized seizures, muscle fasciculations (especially in facial muscles), myoclonic head bobbing movements, and weakness. In one retrospective report involving 29 dogs, dementia was more common in dogs with chronic renal disease, while seizures were more commonly associated with acute renal failure [220]. Laboratory studies reveal increased levels of blood urea nitrogen and creatinine. Renal lesions that have been reported include nephrosclerosis, nephrocalcinosis, peritubular fibrosis, tubular degeneration, pyelonephritis, renal infarction, and hydronephrosis [219,249]. In this report, parathyroid hyperplasia was present in one dog, while no gross or microscopic lesions were seen in the brain of 2 dogs euthanized [219]. The cause of uremic encephalopathy is presently unknown. Suggested mechanisms include depressed cerebral oxygen consumption, cerebral hypoxia, increased brain calcium levels, and increased blood levels of parathyroid hormone (PTH). In experimental uremia in dogs, increased brain calcium levels have been associated with an increase in the serum PTH levels, while administration of PTH to normal dogs produced EEG changes similar to those seen in uremic animals [221]. The EEG abnormalities, as well as the increased brain calcium, could be prevented by performing a parathyroidectomy before the induction of uremia. Serum calcitriol levels (1,25-dihydroxyvitamin D) are reduced in animals with renal failure [222]. The accumulation of toxic organic acids as a possible mechanism of UE is not supported by findings of normal acid-base balance in the CSF, blood, brain, and skeletal muscle of uremic dogs [223]. Water, osmolality, and electrolyte abnormalities do not appear to play a role in the

development of UE in people [1]. Furthermore, clinical signs in dogs are probably not related to hypocalcemia and hypocalcemic tetany due to renal failure, since the metabolic acidosis of uremia tends to maintain the ionized calcium fraction at normal or increased levels [219] (see Hypocalcemia). A recent study suggests that several guanidine compounds (GCs) may play an important role in the etiology of uremic encephalopathy in people, including creatinine, guanidine, guanidinosuccinic acid, and methylguanidine [224]. The excitatory effects of uremic GCs on the central nervous system may be explained by the activation of N-methyl-D-aspartate (NMDA) receptors and concomitant inhibition of GABA-A receptors, and other depolarizing effects. Prognosis for animals in renal failure would appear to be guarded, although earlier research studies indicate that calcitriol, at 1.5 to 3.4 ng/kg/day PO, lowers serum levels of PTH, reverses neurological depression in dogs and cats with chronic uremia, and has a salutary effects on the dog's or cat's sense of well being, appetite, activity, strength, and lifespan [225,226]. Low doses of calcitriol are most effective when started early in uremia before the advanced stages of renal secondary hyperparathyroidism. Serum phosphate levels must be normalized before initiating calcitriol therapy because hyperphosphatemia enhances the tendency for calcitriol to promote renal mineralization and injury [222]. Other treatments should be aimed at the causes of the acute or chronic renal failure, such as correction of hypercalcemia, administration of antibiotics/antimycotics to eliminate bacterial/mycotic infections, removal of lesions (e.g., tumors, uroliths) causing obstructive uropathy, and correction of abnormal renal perfusion that has caused ischemic renal lesions [222]. Hemodialysis, peritoneal dialysis, and renal transplantation are also available treatment strategies. Note that rapid hemodialysis of uremic animals may induce a syndrome characterized by increased CSF pressure, grand mal seizures, and EEG abnormalities [223]. There is a fall in pH and bicarbonate concentration in CSF, and brain osmolality exceeds that of plasma, resulting in a net movement of water into the brain (cerebral edema). This syndrome has been called experimental dialysis disequilibrium syndrome.

### **Miscellaneous Metabolic Disorders**

**Acidosis** - Acidosis secondary to respiratory or metabolic disorders may lead to cerebral vasodilation, increased cerebral blood flow, and sometimes increased intracranial pressure. Neurological signs of CSF acidosis including altered mentation, delirium, and coma [12], and usually result from increased blood levels of CO<sub>2</sub>, which readily crosses the blood-brain-barrier leading to CO<sub>2</sub> narcosis, rather than from metabolic acidosis [1]. In patients with metabolic acidosis, CSF pH decreases slowly and usually does not reach blood pH levels [227]. Treatment should be directed at the underlying cause of the acidosis. A transient paradoxical CSF acidosis may follow administration of bicarbonate [16,227].

**Alkalosis** - Hyperventilation can lead to hypocapnea, respiratory alkalosis, cerebral vasoconstriction, decreased cerebral blood flow, reduced availability of oxygen, a reduction in ionized serum calcium levels, and hypophosphatemia [1,227]. Signs may include confusion and disorientation [12]. Metabolic alkalosis commonly accompanies hypokalemia as a result of translocation of hydrogen ions: as intracellular potassium moves out of cells down the concentration gradient, hydrogen ions (and sodium) shift into cells, causing extracellular alkalosis.

**Hyperthyroidism** - Hypothyroidism in cats may be associated with hyperactivity (hyperkinesis) characterized by pacing, circling, or restlessness, and variable personality changes including anxiety, confusion, and aggression [228-231]. Focal and generalized seizures may also be seen [230]. Neuromuscular signs attributable to hyperthyroidism include weakness, neck ventroflexion, decreased ability to jump, fatigue after physical activity, muscle tremors, nonspecific gait disturbances, and collapse [230]. Some or all of these neuromuscular signs might be related to hypokalemia [232](see hypokalemic myopathy). The pathophysiology of these manifestations is presently unknown, although perturbations in central and peripheral beta adrenergic tone may play a role [1]. Weight loss, increased heart rate, and hyperactivity has been reported in an adult dog with hyperthyroidism and a thyroid neoplasm [244].

**Hypophosphatemia** - Severe hypophosphatemia (i.e., serum inorganic phosphate concentration < 1 mg/dl) occurs infrequently in animals [17,233,234]. It is most often associated with diabetic ketoacidosis (DKA) (see above) in small animals, especially in cats [16]. Hypophosphatemia results from urinary loss of phosphate associated with the osmotic diuresis and replacement fluid therapy in animals with DKA and from insulin-induced movement of phosphate into cells (note that phosphate shifts between the intracellular and extracellular compartments in a similar manner as potassium)[5]. In addition, phosphate depletion may be caused by decreased intake from anorexia and vomiting, and translocation following alkali administration [16]. Other conditions associated with hypophosphatemia in small animals include hyperadrenocorticism, hyperparathyroidism (primary and pseudo), and hypothermia [233]. Respiratory alkalosis associated with hyperventilation will also cause phosphate to move into the intracellular space resulting in hypophosphatemia [233]. Phosphate is necessary for the production of 2,3 diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP); both are important for normal cellular metabolism. When serum inorganic phosphate levels fall below 1 mg/dl, high energy

demanding body cells such as red blood cells, muscle cells (skeletal muscle and cardiac), and brain cells may be preferentially affected with subsequent development of hemolytic anemia, seizures, altered mentation, cardiomyopathy, and skeletal muscle weakness/rhabdomyolysis [16,233]. Note that severe hypophosphatemia may be clinically silent [3]. Treatment in most cases usually involves correction of the underlying cause of the hypophosphatemia; however, in severe cases (e.g. when serum inorganic phosphate levels < 1 mg/dl), parenteral phosphate therapy (e.g., sodium or potassium phosphate solutions) is recommended at a dosage of 0.01 to 0.03 mmol phosphate/kg/h for six hours, before rechecking serum inorganic phosphate levels [5]. A caveat of phosphate therapy is potential risk of deposition of insoluble calcium phosphate into soft tissues and hypocalcemia [5,16,234].

**Hypercalcemia** - Hypercalcemia occurs when serum calcium (from bone resorption or from gastrointestinal absorption) exceeds calciuresis [1]. Physiological hypercalcemia refers to ionized calcium levels increased above their normal range (e.g., > 5mg/dL). Myriad clinical signs associated with hypercalcemia include heart failure, unexplained shock, gastrointestinal disturbances (e.g., vomiting, constipation), renal failure, abdominal pain, tachypnea, restlessness, weakness, hyporeflexia, listlessness, depression, obtundation, and coma [227,235]. Causes of hypercalcemia include primary hyperparathyroidism, hypercalcemia of malignancy, neoplastic bony metastases, vitamin D toxicity, hypoadrenocorticism, and renal failure (acute or chronic) [236]. Paraneoplastic hypercalcemia has been seen with a variety of tumors in dogs and cats including lymphosarcoma/T-cell lymphomas, lymphocytic leukemia, myeloproliferative diseases, and myeloma, as well as solid tumors with metastasis to bone (e.g., nasal, pancreatic, pulmonary carcinomas) and without bony metastases (anal sac apocrine gland adenocarcinoma, malignant melanoma, squamous cell carcinoma, thyroid adenocarcinoma, pulmonary carcinoma, pancreatic adenocarcinoma, and fibrosarcoma [236,245-248]. Treatment should be aimed at the underlying cause of the hypercalcemia, e.g., platinum chemotherapy in canine apocrine gland carcinoma [245]. Calciuresis is promoted with intravenous fluid therapy (e.g., using 0.9% saline at 10 ml/kg bolus over 15 minutes ) and furosemide (1 mg/kg/hour) [227,235,236]. Lowering serum ionized calcium using sodium bicarbonate or sodium phosphate should be avoided due to calcium precipitation into soft tissue and potentially compromising major organs [235].

**Potassium Disorders** - Hypokalemia and hyperkalemia in animals and people are usually not associated with metabolic encephalopathies [1,12]. These disorders are more typically associated with neuromuscular disorders (see hyperkalemic myopathy and hypokalemic myopathy). The major complication of hyperkalemia (usually with serum levels > 7 mEq/L) is cardiac toxicity with irregularities in the EKG, arrhythmias, and/or cardiac arrest [237].

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## Neurotoxic Disorders (6-Feb-2003)

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### Introduction

Neurotoxicity in dogs and cats may result from myriad agents, including metals, pesticides, solvents and other chemicals, and bacterial, animal, and plant-derived toxins, as well as therapeutic agents [1]. Drug-induced toxicity may be caused by overdosage, undesirable side effects, or accidental exposure, usually ingestion. In one study [2], the most commonly reported toxins were: lindane-based insecticides (HCB, hexachlorocyclohexane, Isotox, Lintox); pyrethrin and pyrethroid insecticides (permethrin, fenvalerate/DEET); chlorpyrifos, strychnine, lead, metaldehyde (in metaldehyde-based molluscicides), and caffeine (e.g., ingestion of caffeine-based stimulants or chocolate which contains caffeine and theobromine). In general, signs of neurotoxicity may include excitation, depression, tremors, clonic-tonic seizures, hyperactivity, ataxia, circling, salivation, hyperthermia, and coma. Treatment involves decontamination where indicated (e.g., bathing/shampooing), inducing emesis (e.g. apomorphine), correction of any fluid and electrolyte imbalances, repeated administration of activated charcoal with a saline cathartic (sodium sulfate is more efficient than magnesium sulfate) or performing gastric lavage to decrease the amount the animal absorbs, and providing demulscents (milk, kaolin-pectin) for any gastrointestinal irritation [3].

Neurotoxic agents have been arbitrarily grouped as follows:

#### Metals

- Lead
- Mercury

#### Automotive products

- Ethylene glycol

#### Solvents/cleansing agents

- Alcohols
- Chlorhexidine
- Hexachlorophene

#### Rodenticides

- Anticoagulant Rodenticides
- Bromethalin
- Strychnine
- Thallium

#### Insecticides, Molluscicides, Repellents

- Amitraz
- Chlorinated Hydrocarbons
- Metaldehyde
- Organophosphates/Carbamates
- Pyrethrins and Pyrethroids

#### Herbicides

- (2-methyl-4-chloro) Phenoxyacetic Acid

#### Plants

- Cyanogenic
- Cycad Palms

#### Bacterial

- Botulism
- Tetanus

#### Animal

- Tick Paralysis
- Toad Toxicity

#### Therapeutic agents/drugs

- Aminoglycosides
- Barbiturates
- Caffeine and other Methylxanthines
- Bromide
- Closantel
- Griseofulvin
- Ivermectin
- Levamisole
- Methionine
- Metoclopramide
- Metronidazole
- Pemoline
- Toluene/Dichlorophen
- Tricyclic Antidepressants
- Vincristine
- Zolpidem
- 5-Fluorouracil
- 5-Hydroxytryptophan

### Alcohols

Widespread utilization of short-chain alcohols in solvents and alcoholic beverages provides small animals with numerous opportunities for exposure [4]. Toxicosis most commonly occurs following ingestion but may also arise from inhalation

and/or dermal absorption. The actions of short-chain alcohols are believed to result from nonspecific interactions with biomembranes altering the function of membrane-bound proteins, including the GABA-A receptor. Onset of signs typically occurs within an hour of exposure and may last for 24 hours. Clinical signs include behavioral changes such as excitability, vocalizing, and incontinence, ataxia, drowsiness, unconsciousness, loss of reflexes, respiratory compromise, respiratory and cardiac arrest, and death. Therefore, general measures for resuscitation should be followed in the initial treatment of severe alcohol toxicosis, including endotracheal intubation, mechanical ventilation, correction of acid base imbalance with bicarbonate (metabolism of alcohols alters the redox state in the liver, leading to hypoglycemia and lactic acidosis in some cases). Activated charcoal (2 g/kg PO) should be given within 3 hours of an alcohol ingestion and skin should be decontaminated.

### **Aminoglycosides**

Aminoglycoside antibiotics can adversely affect auditory and vestibular mechanisms, especially after prolonged administration of large amounts of the drugs [5]. These drugs concentrate in perilymph and endolymph, thus exposing the cochlear hair cells to high concentrations of the antibiotic agents. While all aminoglycoside antibiotics can damage auditory and vestibular receptors, streptomycin and gentomycin have their greatest effects on the vestibular system, whereas, neomycin, kanamycin, tobramycin, and amikacin sulfate produce more damage to the auditory peripheral receptors [6]. The toxic effects of these drugs are heightened if the tympanic membrane is perforated. However, in one experimental study, gentamicin sulfate did not induce detectable alteration of cochlear or vestibular function in dogs with intact tympanic membranes or after experimental bilateral myringotomy [7]. In other experimental studies, ototoxicity of aminoglycosides may be enhanced by loop diuretics [8], while the severity of ototoxic side-effects can be influenced by nutritional factors [9].

### **Amitraz**

Amitraz, an alpha-adrenergic agonist and a weak monoamine oxidase inhibitor, may induce sedation, depression, ataxia, and muscle weakness in dogs following excessive exposure, such as application to the skin for *Demodex* control and ingestion of tick collars [10]. Other signs may include hypertension, mydriasis, hypothermia, bradycardia, hyperglycemia, hypoperistalsis, vasoconstriction, vomiting, and diarrhea [11-13]. I have also seen brief, generalized seizures in our own Welsh Corgi following treatment for demodicosis. Nerve conduction studies are normal [13]. Treatment with yohimbine at 0.1 mg/kg IV normally reverses the signs. It has been reported that signs can be reversed by low doses of atipamezole (50 µg/kg, IM), a potent alpha 2-antagonist, within 10 minutes after injection [12].

### **Anticoagulant Rodenticides**

A variety of anticoagulant rodenticides are available with one of the best known being warfarin. These agents interfere with vitamin K<sub>1</sub> hydroquinone recycling in the liver leading to impaired synthesis of functional forms of clotting factors II, VII, IX, and X, and development of coagulopathies/bleeding [220]. Intrathecal or intrameningeal hemorrhage may lead to ataxia, stiffness, or seizures. Diagnosis may be made using common coagulation tests (bleeding time, blood clotting time, activated clotting time, prothrombin time, and activated partial thromboplastin time). The PIVKA test may also be useful in identifying a vitamin K<sub>1</sub>-responsive coagulopathy. Treatment may involve use of fresh frozen plasma (at 9 mL/kg) or whole blood (at 20 mL/kg) followed by oral vitamin K<sub>1</sub> at a rate of 2.5 mg/kg sid for 2 to 4 weeks.

### **Barbiturates**

Barbiturates inhibit calcium accumulation in neural tissues and thereby inhibit the release of neurotransmitters [1]. Barbiturate anesthetics produce profound respiratory and CNS depression, general anesthesia, hypothermia, hypotension, shock, cyanosis, and coma [1]. Phenobarbital may have several side-effects that include sedation, nystagmus, ataxia, behavioral changes, hyperexcitability, polydipsia, polyuria, and polyphagia [10]. Signs may disappear after several weeks of treatment as animals adapt to the dosage. The hyperexcitability may be difficult to manage and may be the limiting factor in the use of phenobarbital [10]. Treatment of barbiturate poisoning involves use of emetics, activated charcoal, gastric lavage, ventilation support, and fluid therapy.

### **Botulism**

Botulism is a disease resulting from the ingestion of spoiled food or carrion containing a preformed exotoxin produced by spores of *Clostridium botulinum*. The neurotoxin associated with canine disease has been reported to be type C [14-21]. Botulism is an uncommon disease in dogs and naturally occurring disease has not been reported in cats [22], although type C botulism has been reported in dairy cattle from feed contaminated with a dead cat [23]. Most cases in dogs appear to result from eating carrion or contaminated raw meat (botulinum toxin is destroyed by heating at 100°C for 10 minutes). The

toxin is absorbed from the stomach and upper intestine, circulates in lymphatics and finds its way to the neuromuscular junction of cholinergic nerves where it blocks pre-synaptic release of acetylcholine [24] leading to generalized motor neuron disease and parasympathetic dysfunction [22]. Clinical signs may occur within hours to several days following ingestion of toxin. Clinical signs reflect a progressive, symmetrical disorder, ranging from mild weakness to severe flaccid tetraplegia with absent spinal reflexes and evidence of weakness in muscles of the face, jaw, pharynx, and esophagus resulting in dysphonia, dysphagia, facial paralysis, and megaesophagus. Mydriasis may be present. Early in the course of the disease, or in mildly affected animals, the gait may be stiff and pelvic limbs may be used in a synchronous, bunny hopping fashion. Presence of keratoconjunctivitis sicca in some dogs suggests autonomic dysfunction. Pain perception remains normal and muscle atrophy is not seen. There is no hyperesthesia [22].

Hematological and biochemical parameters are unaffected. Electrodiagnostic studies may reveal a low amplitude of the evoked muscle action potential, decrease in amplitude of the compound muscle action potential with slow repetitive stimulation, slowing of motor and sensory nerve conduction velocities, and sometimes, fibrillation potentials and positive sharp waves, especially in distal limb muscles [25]. These latter changes indicate peripheral nerve dysfunction through some as yet unknown action of the botulinum toxin. Nerve conduction velocity and amplitude can return to normal as clinical improvement occurs.

Diagnosis is suggested by historical, clinical, and electrodiagnostic data. It is confirmed by identification of the toxin in the material ingested or in serum, feces, or vomitus of an affected animal with type-specific antitoxin using the neutralization test in mice [22,26]. ELISA has also been used [27]. Serum should be collected early in the course of the disease [21]. In one report, *Clostridium botulinum* type C was still present in feces and a low toxin titer persisted for 114 days after ingestion of a contaminated duck carcass [20].

The prognosis is usually favorable in dogs, with recovery occurring within 1 to 3 weeks [22], although some affected dogs are euthanized due to other clinical complications [28]. Treatment is primarily supportive. Severely affected animals should be monitored closely to avoid the potential complications of inhalation pneumonia, respiratory paralysis, and urinary tract infections. Padding should be used for recumbent animals, along with assistance with drinking and eating. Penicillin or metronidazole may be used to reduce intestinal clostridial numbers. The use of botulinum antitoxin is controversial [22]. Note that the history, clinical signs, and pattern of onset of lasalocid-induced toxicosis in dogs are similar to those reported for botulism [29].

### **Bromethalin**

Bromethalin toxicosis (e.g., in bromethalin-containing rodenticides) in dogs induces a variety of neurological signs. Dogs given a single oral dose of bromethalin at 6.25 mg/kg developed a toxic syndrome characterized by hyperexcitability, tremors, focal motor and generalized seizures, depression, and death within 15 - 63 hours after bromethalin administration. Clinical signs were dose-dependent, with signs of hind limb ataxia, and/or paresis, and/or CNS depression noted following lower doses. CSF pressure may be increased. Predominant abnormal EEG changes included spike and spike-and-wave EEG patterns, high voltage slow wave (50 - 150 microV, 1 - 6 Hz) activity, photoconvulsive or photoparoxysmal irritative responses, and marked voltage depression (dominant activity less than 10 microV) in all leads [30]. Gross lesions included mild cerebral edema and mild pulmonary congestion. Histologic lesions included diffuse white matter spongiosis, mild microgliosis, optic nerve vacuolation, mild thickening of Bowman's capsule, and occasional splenic megakaryocytes. Ultramicroscopic examination of midbrain stem revealed occasional swollen axons, intramyelinic vacuolization, and myelin splitting at the intraperiod line. Bromethalin was detected in kidney, liver, fat, and brain tissues, using gas chromatography with electron capture detection. Photodegradation of extracted bromethalin may limit accurate quantification of tissue residues. In experimental trials, repeated oral administration (e.g. 3 times daily) of a superactivated charcoal/sorbitol product (Superchar-Vet Liquid®) is reportedly an effective therapy [31,32]. In addition, dexamethasone at 2 mg/kg IV every 6 hours, or prednisolone at 2 to 6 mg/kg, PO, daily, and mannitol solution at 500 mg/kg, IV, every 6 hours to reduce cerebral edema, is recommended [11]. Bromethalin-based rodenticides are also highly neurotoxic to cats. Signs include tetraparesis/paralysis with extensor rigidity, depression, coma, focal motor seizures, anisocoria, positional nystagmus, and opisthotonus [33].

### **Bromide**

Potassium bromide (BR) is a commonly used antiepileptic drug. The recommended oral dosage for BR is 20 - 40 (60) mg/kg /day (one daily dosage). The therapeutic range of BR in dogs is 100 - 200 mg/dl when potassium bromide is used as an add-on drug and 250 - 300 mg/dl when used as monotherapy (see Epilepsy). A variety of neurological signs have been reported in dogs attributable to bromide toxicosis (bromism) including anisocoria, muscle pain, hyporeflexia, hind limb weakness, ataxia, disorientation, depression, recumbency, and stupor. Presumably toxicosis might be expected in some dogs when serum levels exceed therapeutic BR concentrations [215,218]. Toxicosis has also been reported in an epileptic dog with renal insufficiency receiving potassium bromide at a dosage of 29 mg/kg /day [219].

## Caffeine

Caffeine is a methylxanthine compound (other related compounds are theophylline, aminophylline, and theobromine) and a CNS stimulant [34]. Methylxanthines enhance catecholamine release and increase calcium entry into cells, and inhibit phosphodiesterase, an enzyme that degrades cyclic AMP (cAMP) [2]. Cardiac acceleration occurs with the increase of cAMP [34]. Intoxication in animals most commonly occurs within several hours following ingestion of chocolate, caffeine-based tablets, or elixirs [1]. One ounce of chocolate contains 5 - 10 mg of caffeine and 35 - 50 mg of theobromine, while baking chocolate is approximately 10 times more toxic [2]. Signs of toxicity in dogs and cats may include vomiting, restlessness, hyperactivity, ataxia, muscle tremors, tachycardia, cardiac arrhythmias, seizures, hyperthermia, polydipsia/polyuria, cyanosis, and coma [1,35,209]. There are usually no histological lesions found in the CNS [2]. Treatment is symptomatic and supportive, including anticonvulsants, antiarrhythmic agents, activated charcoal, and fluids.

## Chlorhexidine

Chlorhexidine is commonly used as an antiseptic and disinfectant. There have been reports of vestibular dysfunction following use of chlorhexidine (0.5%) or chlorhexidine (1.5%)/cetrimide (15%) in treating otitis externa in dogs and cats with perforated tympanic membranes [36]. Pathological findings included loss of sensory epithelium and fibrosis, and degeneration of afferent nerve terminals and the hair cells in the organ of Corti [1,36]. There is no specific treatment for this toxicosis although immediate flushing of the middle ear with saline may be beneficial [36]. Interestingly, a solution containing 0.2% chlorhexidine did not induce vestibular or cochlear neurotoxicity following installation (over a 3-week period) into the external ear canals of dogs with intact and surgically perforated tympanic membranes [37].

## Chlorinated Hydrocarbon Toxicity

Chlorinated hydrocarbon compounds (e.g., endrin, aldrin, dieldrin, heptachlor, lindane, DDT) are used for prevention and control of insect infestations around farms, homes, and on animals, although regulatory agencies have banned the use of many of these insecticides because of accumulating tissue residues and environmental persistence [11]. Dogs and cats may be poisoned by ingestion, inhalation, or absorption through the skin when the insecticide is applied topically [38]. Endosulfan is presently used for garden or farm use and is highly toxic to cats and has been used maliciously to kill dogs [11]. Chlorinated hydrocarbon insecticides are considered to be non-specific stimulants of the central nervous system [38]. Clinical signs can include anxiety, hysteria, facial muscular spasms, jaw champing, spastic gait, ataxia, mydriasis, salivation, and severe generalized seizures. External stimuli may precipitate seizures. Body temperature will usually increase significantly as a result of the seizures. Death may occur within minutes or hours, after several days, or not at all. Neuropathological changes are usually absent [39].

A presumptive diagnosis is based on historical data of recent exposure to the toxin and clinical signs. Prognosis is guarded. Signs of acute toxicosis usually abate in 1 to 2 days. Complete recovery may take weeks. Treatment is symptomatic since there is no known antidote. Seizures may be controlled using intravenous anesthetic barbiturates, given to effect. Purgatives and/or gastric lavage will help remove residual toxin ingested, but maximum benefit is to be expected only during the initial 2 hours after exposure. Soap and water scrubs are indicated for animals exposed by the dermal route. Hyperthermic animals may be bathed in cool water. Forced diuresis with 5% mannitol in 0.9% sodium chloride can enhance urinary excretion.

## Closantel

Closantel, a salicylanide derivative and potent uncoupler of mitochondrial oxidative phosphorylation, is primarily used as an anthelmintic against nematodes, trematodes and some arthropods in ruminants. It has also been used in treating dogs infected with demodectic mange and *ancylostoma caninum*. Acute closantel intoxication has been reported in a 13 month old dog that accidentally received 6 times the normal recommended dosage (normal dosage is 5 mg/kg subcutaneously followed by 2.5 mg/kg every week until cessation of clinical signs) [210]. Clinical signs of intoxication included depression, blindness, bilateral mydriatic pupils unresponsive to light stimulation, hearing deficit, pelvic limb weakness, hypotonicity, hypersalivation, emesis, diarrhea, and polydipsia/polyuria. Fundic exam revealed markedly swollen optic disks, small papillary/peripapillary hemorrhages, and tapetal hyperreflectivity. Biochemical serum studies revealed marked increase in liver enzymes, muscle CK, and total bilirubin, but decrease in total protein and albumin. The results of clinical and diagnostic findings suggested optic neuritis, myopathy, retinal degeneration, and hepatotoxicosis. Initial supportive treatment included fluid therapy, forced feeding a semifluid diet (Canine/Feline a/d ®, Hills), and prednisolone 2 mg/kg PO bid (followed by alternate day therapy for 1 week and progressive reduction over the ensuing 2 weeks) for the optic neuritis. In order to bind any free closantel (the toxic fraction, since most closantel is bound to plasma proteins, and almost exclusively to albumin), a daily intravenous infusion of 20% albumin was administered (1 ml/kg/day). The dog responded over several weeks and biochemical values returned to normal. Three months after intoxication, the dog appeared clinically normal, although blindness persisted. The histopathology associated with closantel poisoning in dogs is uncertain; however, in sheep with closantel intoxication, spongiform changes are commonly found in the brain, including optic tracts/fasciculi,



and neuronal loss in the ganglion cell layer and outer layer of the retina. The chances of chronic toxicity developing in dogs receiving closantel over several months appears to be quite low.

### **Cyanogenic Plants**

Seizures and semicoma, accompanied by bradycardia, pale and cyanotic mucous membranes, pulmonary congestion, vomiting, and frequent defecation were observed in an 11-week-old puppy after consumption of leaves and stems from the cyanogenic shrub, heavenly bamboo (*Nandina domestica*) [40]. Treatment was supportive, including intubation and oxygenation, epinephrine (1:10,000, IM), prednisolone sodium succinate (100 mg, IV), furosemide (12.5 mg, IV), and ampicillin trihydrate (50 mg, SC). The following morning, the puppy appeared normal.

### **Cycad Palms**

Cycad palms occur in dry sandy soils of tropical and subtropical regions. Ingestion of cycads (also known as sago palms) can result in toxicosis in animals. In a recent survey of 60 dogs with evidence of cycad ingestion, approximately 90% of the dogs were from the southern United States, 39% ingested seeds, 95% developed liver and gastrointestinal tract problems, and 53% had abnormal neurologic signs, including weakness, ataxia, depression, proprioceptive deficits, coma, or seizures [41]. It is not known if the neurological signs were secondary to liver damage or to neurotoxins. High serum bilirubin concentration and alkaline phosphatase and alanine aminotransferase activities were the most common serum biochemical abnormalities. Although clinical signs were observed within 1 day, laboratory values did not change for 24 to 48 hours after cycad ingestion. Mortality rate was 32%, with the remaining dogs responding well to treatment and supportive care such as, emesis, repeated doses of activated charcoal, fluid therapy (e.g., 5% dextrose IV), and seizure control. Sucralfate at 0.5 - 1.0 g, PO, tid, may be used if vomiting is severe or if GI ulceration develops. Dogs ingesting seeds were likely to develop more serious problems.

### **Ethylene Glycol Toxicity**

Ethylene glycol (EG) is a commercial antifreeze automotive product with limited toxicity, but its metabolites, including glycolic acid are extremely toxic to dogs and cats. In a recent report from the ASPCA National Animal Poison Control Center, exposures were commonly (57%) from container spill, engine flush, or engine leak and were in or around the home (66%) [42]. Interestingly, among cases with a known final outcome, 59% did not show clinical signs and death/euthanasia was reported in 28%. In an earlier study, a mortality rate of 43% was reported in dogs and cats [43]. As little as 1 tablespoonful of 50:50 radiator fluid can be lethal in cats, while 4.5 ounces may be lethal in a 20-pound dog [11]. Signs of depression, vomiting, knuckling, ataxia, seizures, and coma may be observed within a few hours of exposure. Affected animals may be hypothermic. The condition is associated with severe metabolic acidosis, serum hyperosmolality, and eventually, renal failure with polydipsia, polyuria, calcium oxalate monohydrate and dihydrate crystalluria, and isosthenuria [44]. Glycolic acid is metabolized to formic acid, oxalic acid and oxalate. The oxalate combines with calcium to form oxalate crystals in renal tubules (especially proximal), urine, and within the lumen or perivascular space of cerebral capillaries [39]. Microscopically, the crystals appear pale yellow and there is evidence of nephrosis with attenuated epithelial cells and dilated tubules [39]. The birefringent crystals may be found in urine after 3 hours in cats and after 5 hours in dogs. Anion gaps > 40 - 50 mEq/L may be diagnostic. A moderate hypocalcemia may be found in serum. Ultrasonographic changes vary from mild to marked increases in renal cortical echogenicity [45]. Ethylene glycol colorimetric spot tests are available for use with urine and serum. A test for rapid (10 min) analysis of biological fluids for EG and glycolic acid also has recently been reported [46].

Treatment consists of administration of activated charcoal and sodium sulfate, correction of dehydration and acidosis, and maintaining fluid therapy. Fomepizole (4-methylpyrazole), an alcohol dehydrogenase inhibitor, is considered safe and effective for dogs if started within 8 hours of exposure [44,47]. The dose is 20 mg/kg, IV, initially as a loading dose, followed by doses of 15, 15, and 5.0 mg/kg at 12, 24, and 36 hours. This drug is not recommended for cats [48]. Instead, 20% ethanol (also an inhibitor of EG metabolism) is given at 5 mL/kg in saline IV, and 5% sodium bicarbonate at 6 mL/kg IV every 6 hours for 5 treatments, then every 8 hours for 4 treatments [11]. For dogs, the ethanol dosage is 5.5 mL/kg in saline IV, together with 8 mL/kg of 5% sodium bicarbonate, IP, each given every 4 hours for 5 treatments, then every 6 hours for 4 treatments. In cases of severe renal failure, peritoneal dialysis and hemodialysis may be options to ameliorate the azotemia, fluid, electrolyte, and acid-base abnormalities [49,50]. Prognosis is guarded. In one study in which EG intoxication was confirmed in 37 dogs, 21 were azotemic or became azotemic within 18 hours after admission, and only 1 of the 21 survived [47]. However, dogs treated with Fomepizole within 8 hours of EG ingestion had a good prognosis. Note that ultrasonographic detection of the "halo" sign (a pattern of greater than normal cortical and medullary echogenicity with persistence of areas of lesser echo intensity at the corticomedullary junction and central medullary regions) in anuric animals with EG intoxication was considered to warrant a grave prognosis.

### **5-Fluorouracil**

5-Fluorouracil (5-FU) is a pyrimidine analog and an antimetabolite. It destroys rapidly dividing cells and is used to treat many neoplastic conditions. 5-FU creams and solutions are used for topical treatment of solar and actinic keratoses and some skin tumors in people [1,51]. In a report of 26 cases of accidental 5-FU ingestions by dogs reviewed from phone calls to the Illinois Animal Poison Information Center from January 1, 1987 to December 31, 1988, 12 were classified as "toxicosis", 13 as "suspected toxicosis", and one as "exposure" [51]. Dogs were the only species involved in 5-FU cases received during this time. Ingestion of more than 20 mg/kg of 5-FU was associated with the development of toxicosis. None of the 12 dogs that ingested oral doses in excess of 43 mg/kg (estimated) survived. Clinical signs associated with 5-FU poisoning in the dog were death, seizures, vomiting (with and without blood), tremors, diarrhea (with and without blood), ataxia, and depression. Cardiac arrhythmias, and respiratory depression have also been noted [51]. Clinical signs generally developed within 45 to 60 minutes after exposure, and deaths occurred 6 to 16 h after ingestion. Hyperesthesia, hyperexcitability, nervousness, muscle tremors, and cerebellar ataxia have also been reported in dogs and cats following intravenous 5-FU treatment or accidental ingestion [1]. Treatment should include dermal decontamination, GI tract decontamination/protection (e.g., sucralfate 0.5 - 1.0 gm, PO, tid), fluid therapy, anticonvulsants (e.g., pentobarbital sodium 3 - 15 mg/kg IV slowly to effect, or phenobarbital 3 - 30 mg/kg IV slowly to effect), and GI protectants. It is recommended that induction of emesis or administration of activated charcoal be delayed until seizures are controlled and the airway protected so as to avoid aspiration [51].

### **Griseofulvin**

Griseofulvin treatment of ringworm in pregnant cats has resulted in multiple congenital malformations in kittens [52]. Malformations of the brain included exencephaly, malformed prosencephalon, caudal displacement, and hydrocephalus. Skeletal malformations included cranium bifidum, spina bifida (C1 through C4, and sacral), abnormal atlantooccipital articulation, cleft palate, absence of maxillae, and lack of tail vertebrae. Cyclopia and anophthalmia with absence of optic nerves and rudimentary optic tracts were also observed. Atresia ani, atresia coli, lack of atrioventricular valves in the heart, and absence of external nares and soft palate were other abnormalities present.

### **Hexachlorophene Toxicity**

Hexachlorophene (pHisoHex ®) is used as a germicide in soaps, shampoos and disinfectant solutions. Dogs and cats may be exposed by percutaneous absorption of hexachlorophene following skin application, or dogs may eat soap containing hexachlorophene [53-57]. Nursing puppies have been poisoned following hexachlorophene application to the mammary glands of the bitch [55]. Clinical signs in dogs are usually characterized by acute onset of tremors, especially of the head, that can increase with excitement. Tremors may disappear during inactivity or sleep. Neuromuscular twitchings, spasms, opisthotonus, severe seizures, and death have been reported in some affected animals [56]. Irreversible visual impairment and permanent mydriasis were reported in Beagles following dermal application of an ointment containing 3% and 10% hexachlorophene over a 12-week period [58]. In cats, dilated pupils, vomiting, weakness, ataxia and spastic or flaccid paralysis, along with signs of hypovolemic shock (hypothermia, pale mucous membranes, tachycardia, tachypnea, and dyspnea) have been reported [53,59]. Significant elevations in cerebrospinal fluid pressure have been recorded in cats following experimental hexachlorophene toxicity [59].

Grossly, mild brain edema has been reported associated with flattening of the cerebral gyri and prolapse of a portion of the cerebellum through the foramen magnum [54,56]. Microscopically, the toxin produces spongiform changes, seen as a vacuolar myelinopathy, in the white matter of the brain, cerebellum and spinal cord, along with astrocytosis and microgliosis [53,56]. Comparative studies have shown that the vacuoles are associated with intramyelinic edema with splitting of myelin sheaths at the intraperiod line [60,62]. Neuronal cell bodies appear to be unaffected. Vacuolar lesions may also be seen in peripheral nerves [39,63]. Lesions in the CNS may regress after exposure to hexachlorophene is stopped [63].

Prognosis is guarded. Some animals recover spontaneously within a few weeks following removal of the exposure to hexachlorophene [55]. Paralyzed cats that have not reached the stage of severe central nervous system depression usually recover if exposure is stopped; however, clinical recovery may take 4 to 6 weeks. Gastric lavage or saline cathartic treatment may help animals that have ingested the toxin. In experimental studies with cats, hexachlorophene toxicosis has been reversed by slow intravenous injection of 30% urea (2 gm/kg) in a 10% aqueous glucose solution [59]. Cats are especially sensitive to phenol intoxication because of their inability to conjugate glucuronic acid with phenolic compounds. Since hexachlorophene is a polychlorinated biphenol, its use in cats should be contraindicated [53]. Barbiturates reportedly are ineffective in controlling seizures in dogs with experimental hexachlorophene toxicity [56].

### **5-Hydroxytryptophan**

5-Hydroxytryptophan (5-HTP) is sold as an over-the-counter dietary supplement. Within target cells of the CNS,

cardiovascular system, GI tract and respiratory tract, 5-HTP is rapidly converted to serotonin. In a recent survey involving 21 dogs with evidence of accidental 5-HTP ingestion, clinical signs of toxicosis, resembling serotonin syndrome in humans, developed in 19 of 21 (90%) dogs. Neurologic signs included seizures, depression, tremors, hyperesthesia, and ataxia. Gastrointestinal tract signs included vomiting or diarrhea, signs of abdominal pain, and hypersalivation. Other clinical signs were hyperthermia and transient blindness. Three dogs died. No important clinical laboratory or necropsy findings were reported. The doses of 5-HTP ingested ranged from 2.5 to 573 mg/kg of body weight; the minimum toxic dose reported was 23.6 mg/kg, and the minimum lethal dose was 128 mg/kg. Onset of signs ranged from 10 minutes to 4 hours after ingestion, and signs lasted up to 36 hours. Of 17 dogs with clinical signs of toxicosis that received prompt and aggressive treatment, 16 recovered. Treatment consisted of decontamination, seizure control, thermoregulation, fluid therapy, and supportive care. Cyproheptadine, a serotonin antagonist, is also recommended at 1.1 mg/kg, PO or rectally, every 1 to 4 hours until signs resolve [64,65].

### **Ivermectin**

Ivermectin, approved for the prevention of canine heartworm infection (at 6 µg/kg, monthly), and believed to be a gamma-aminobutyric acid (GABA) agonist, can produce severe CNS dysfunction in some dogs. In mammals, GABA acts as an inhibitory neurotransmitter at pre- and postsynaptic neurons within the CNS. Signs include depression/disorientation, muscle fasciculations, ataxia, dilated pupils, drooling, rarely seizures, and coma. Mydriasis, depressed menace response, and apparent blindness (reversible with time) may also be observed, along with vomiting, diarrhea, hyperthermia, bradycardia, and sinus arrhythmia [1]. Collies appear idiosyncratically sensitive to the drug [66-68], although toxicosis has been seen in other breeds [69], perhaps associated with the blood-brain barrier acting as an ineffective ivermectin barrier [1]. Treatment is supportive, including activated charcoal and a saline cathartic, fluids, shock doses of corticosteroids (in severely affected dogs), and picrotoxin and physostigmine only in comatose dogs [1]. It has been reported that ivermectin and milbemycin commercial formulations have similar margins of safety and that milbemycin toxicosis appears to be dose-dependent in Collies with a demonstrated sensitivity to ivermectin [70].

### **Lead Poisoning**

Accidental lead poisoning is one of the more common intoxications of dogs and cats [71-80]. It may occur from many sources including linoleum, putty, roofing felt, golf balls, old car batteries, lead weights, ingestion of contaminated soil, improperly glazed ceramic water bowls, and toys; however, lead-based paints are the most frequent source of poisoning [78,81]. Lead is believed to inhibit sulfhydryl groups of essential enzymes of cellular metabolism. One important consequence of this is inhibition of heme synthesis resulting in the circulation of immature erythrocytes [82]. Dietary factors, such as high-fat- low-calcium diets, may facilitate absorption of lead from the alimentary tract [83]. The majority of absorbed lead is deposited in bones, followed by liver and kidney, brain and spinal cord [84]. Lead can disrupt the blood-brain barrier by damaging capillary endothelial cells with resultant cerebral edema and hemorrhage. In the brain, morphological changes range from diffuse capillary proliferation to status spongiosus and cerebral cortical necrosis. In studies of experimental lead toxicosis of dogs, microscopic lesions were present in up to 89% of the lead-treated dogs [85,86]. Cerebrocortical lesions comprising spongiosis, vascular hypertrophy and gliosis predominated. These lesions were bilateral, had a predilection for gyri and were located mainly in the parietal and frontal cortex. There were bilaterally symmetrical spongiform changes in the brain stem. The cerebellum had spongiform changes in the roof nuclei and in the lingula there was spongiosis of the Purkinje cell layer and vacuolation of Purkinje cells. Axonal degeneration was evident in a sciatic nerve of only one dog. While peripheral neuropathy may occur sporadically with spontaneous lead poisoning, the inability to experimentally produce a polyneuropathy in dogs given chronic oral low level lead in another study [87], further suggests that dogs may be resistant to the toxic neuropathic effects of lead.

Lead poisoning is more commonly reported in dogs than cats [77]. Affected animals may be of any age (e.g., from 8 weeks to 16 years). In case reports of lead toxicoses from 2 major animal poison control centers in Europe and North America, 60% of dogs were less than 2 years old [81]. The incidence is reportedly higher in summer and early fall [81]. Clinical signs of central nervous system dysfunction usually are preceded or accompanied by gastrointestinal malfunction [74,78]. Signs may be acute or chronic. The most common gastrointestinal signs in dogs and cats are vomiting, anorexia, diarrhea, and in some animals, abdominal pain. Common neurological signs in dogs and cats include depression, generalized seizures, hysteria (barking and/or whining continuously, aimless running and snapping at objects), ataxia, blindness, head pressing, and jaw champing. Abdominal pain and hysteria may be more common in animals less than 1 year of age. Megaesophagus and partial laryngeal paralysis, believed to be due to lead-associated neuropathy, have been seen in a cat [88].

Megaesophagus may also be observed in dogs with lead poisoning. In some cats, clinical signs may be non-specific (e.g., weight loss). Low-level lead intake in young dogs can cause an early increase in blood pressure [89].

Diagnosis is suggested by finding rubricytosis and numerous nucleated erythrocytes in a stained blood smear [90]. The presence of basophilic stippling in red blood cells, anemia, increased packed cell volume, presence of diffuse radiopaque

material in the gastrointestinal tract, and radiopaque bands in x-rays of long bone metaphyses of young dogs [84], also supports the diagnosis (chronic low dose lead intoxication results in bone storage and altered normal bone physiology [91]). Elevated urinary levels of delta aminolevulinic acid has been reported to have limited value as a diagnostic aid in canine lead poisoning [75,92]. Furthermore, recent studies suggest that theta-aminolevulinic acid dehydratase and zinc protoporphyrin were of poor predictive diagnostic value as markers of lead intoxication in dogs [93,94]. In some animals, leukocytosis, elevated liver enzyme levels, and increased serum concentrations of glucose and cholesterol may be found. Levels of 40 µg or more of lead/100 ml of whole blood is considered definitively diagnostic of lead poisoning [71,77]. There is no direct correlation between severity of clinical signs and blood level content. Electroencephalographic changes reported in nonsedated dogs were marked by intermittent high-amplitude slow wave activity [95]. Treatment with the chelating agent, calcium disodium ethylene diamine tetraacetate (EDTA), using a dose of 25 mg/kg IV, qid for 2 to 5 days, often results in rapid recovery within 36 to 48 hours. Oral administration (same dosage) has also been effective [96]. Alternatively, oral penicillamine may be given in a dose of 100 mg/kg, daily, for 1 to 2 weeks. Treatment is repeated over another 5-day period if signs persist. The prognosis is favorable in the majority of lead poisoning cases treated with chelating agents [78,97]. Recent studies in dogs with naturally acquired lead poisoning indicated that succimer (meso-2,3-dimercaptosuccinic acid), administered orally for 10 days (10 mg/kg of body weight, PO, q 8 h), also effectively reduced blood lead concentrations and eliminated clinical signs of lead poisoning [98]. Succimer is also effective in cats [214]. Succimer may also be given rectally as a solution in patients that are vomiting.

### **Levamisole**

Levamisole is used as an anthelmintic, microfilaricide, and immunostimulant [1,99,100]. Clinical signs of toxicity may be seen at approximately 4 times the normal therapeutic dose (which is 10 to 11 mg/kg), although toxicity has been reported following a single oral dose of levamisole hydrochloride given at the rate of 12 mg/kg [101]. Levamisole is a nicotine-like ganglionic stimulant producing both muscarinic and nicotinic effects at cholinergic receptors [1]. Clinical signs and lesions of levamisole toxicosis include: nausea, vomiting, increased salivation, frequent urination and defecation, colic, dizziness, headache, muscle tremors, ataxia, anxiety, hyperesthesia with irritability, clonic convulsions, depression, rapid respiration, dyspnea, cardiac arrhythmias, prostration, collapse, hemorrhages in the subepicardium and thalamus, enteritis, hepatic degeneration and necrosis, and splenic congestion. Most of these signs and lesions are similar to those observed in nicotine poisoning [102]. Levamisole causes an electroencephalographic arousal and multiple foci of EEG irritation [101,102]. Treatment is largely supportive, including GI tract decontamination, seizure control, fluid therapy, and ventilation support [1].

### **Mercury Poisoning**

Dogs and cats are susceptible to mercury poisoning [39,103-105] a condition that has been termed Minamata disease (methyl mercury poisoning) in people. Elemental mercury is transported in blood plasma, proteins and hemoglobin, and may be incorporated rapidly into the brain [106]. While rarely seen in clinical practice, methylmercury (MM) poisoning or methylmercurialism usually occurs after consumption of contaminated fish, especially in cats [107-109] although it has also been reported in dogs [110]. Neurologic signs in dogs and cats following oral exposure have included abnormal symmetrical use of pelvic limbs, hypermetria, ataxia, paresis, abducted pelvic limbs, loss of postural reactions, proprioceptive impairment, blindness, opisthotonus, grand mal convulsions and terminal recumbency [111]. Serum biochemical findings were limited to hypercholesterolemia in dogs. Significant species difference in susceptibility to MM-induced neuronal lesions was the relative resistance of the feline spinal cord, canine cerebellar cortex and canine peripheral nervous system. Subacute exposure produced marked cerebral cortical involvement in dogs and cats, marked cerebellar cortical lesions, marked CNS perivascular inflammatory cell cuffing in cats, marked leptomeningitis in dogs and moderate lesions in the brain stem and cerebellar roof nuclei in both species. Chronic exposure of a dog to 120.4 µg Hg/kg/day for 55 weeks produced a marked loss of neurons and reactive astrocytosis in the cerebral cortex in the absence of clinical signs of toxicity. Twice weekly exposure to 0.64 mg Hg/kg as MM for 6 to 9 weeks in 5 dogs produced milder clinical signs, hypercholesterolemia, lipoproteinemia, and hydrocephalus. Neuronal loss and gliosis were most severe in the cerebral cortex with minimal involvement of the brain stem. Cerebellar lesions observed in cats include focal atrophy of the granular layer, focal spongiosis of the molecular layer and degeneration and loss of Purkinje cells in the cerebellum [112]. Demyelination in the fiber tracts of the dorsal funiculus, mainly the fasciculus cuneatus and in the lateral and ventral corticospinal tracts were also noted [112]. Terminal blood MM levels were in excess of 18 µg/ml, while brain methylmercury levels ranged from 21.0 to 28.4 µg/g. The liver and kidney contained the highest total levels of mercury of 50 to 80 µg/g, of which 23 to 37% was inorganic [112]. Increased levels of mercury in the brain does not necessarily result in behavior abnormalities or pathology [113]. In acute exposure to ingested mercury salts, oral administration of milk and eggs to bind mercury to protein has been recommended [11].

## **Metaldehyde**

Metaldehyde toxicosis usually follows ingestion of metaldehyde-based molluscicides [2]. The incidence of toxicosis is more common in coastal and low-lying areas. Metaldehyde is degraded to various aldehydes in the stomach which may give a formaldehyde odor to the contents [114]. Signs include tachycardia, salivation, tremors, vomiting, hyperesthesia, nystagmus (especially in cats), ataxia, opisthotonus and seizures, hyperthermia, diarrhea, and depression. Death from respiratory failure may follow from 4 to 24 hours after ingestion. Delayed deaths may follow liver failure (after 3 to 4 days). Stomach contents should be submitted in suspected poisonings. Treatment includes activated charcoal, anticonvulsants, and fluid therapy with sodium lactate to correct the severe acidosis that develops in poisoned animals [11].

## **Methionine**

Methionine is an essential amino acid and nutrient, a lipotrope, and a urine acidifier [65]. It has been used as a nutritional supplement in food animals. Accidental ingestion may lead to neurotoxicity and metabolic acidosis. The toxicity of methionine is partially related to its metabolism to ammonia and to increased production of mercaptan-like compounds. Toxicity is especially apparent in dogs with pre-existing liver disease. Signs include excessive salivation and vomiting, ataxia, depression, lethargy, circling, head pressing, aimless pacing, aggression, somnolence, blindness, seizures, stupor and coma [1]. In experimental studies, cats given DL-methionine (0.5 to 1 g/kg of body weight/day) developed severe hemolytic anemia and excessive oxidation of hemoglobin leading to a marked increase of methemoglobin concentration and Heinz-body formation [115]. Treatment is supportive, including emetics, activated charcoal, saline cathartic, and fluids containing bicarbonate [1].

## **(2-Methyl-4-chloro) Phenoxyacetic Acid**

Ten hours following ingestion of an accidentally spilled herbicide that contained an octanoic acid ester of bromoxynil (3,5-dibromo-4-hydroxybenzonitrile) and an isooctyl ester of (2-methyl-4-chloro) phenoxyacetic acid (MCPA), an 8 year old Golden Retriever showed signs of vomiting, abdominal pain on palpation, ataxia, anorexia, and generalized weakness [116]. Appendicular muscles were firm on palpation and persistent muscle contraction (myotonia > 1 minute duration) was found on muscle percussion, using a reflex hammer. Electrical activity indicative of myotonia was identified on EMG evaluation. With supportive treatment, the dog eventually recovered from suspected MCPA toxicosis.

## **Metoclopramide**

Metoclopramide, a derivative of para-aminobenzoic acid, has GI stimulatory and antiemetic properties, and has been employed clinically for gastric stasis disorders, gastroesophageal reflux, vomiting, nausea, and to allow intubation of the small intestine [117]. In the CNS, metoclopramide antagonizes dopamine at receptor sites and also sensitizes tissues to the effects of acetylcholine. Neurotoxicity may occur at therapeutic levels with dogs and cats showing signs of movement disorders such as slow to rapid twisting movements of the face, neck, trunk or limbs, as well as CNS depression, nervousness, restlessness, or frenzied behavior (especially in cats) [1]. Signs usually resolve within a few days after terminating metoclopramide medication. Diphenhydramine (2 - 4 mg/kg PO, IM, or IV, tid) may reduce the movement disorders. Most of the signs disappear in 2 - 3 days after stopping medication [10].

## **Metronidazole**

Metronidazole is used in small animals for treating giardiasis, trichomoniasis, and certain anaerobic infections. It appears that most neurotoxicoses in dogs and cats result from long term administration, and usually at high dose rates (e.g., exceeding 66 mg/kg/day, in dogs) [1]. In one report, five dogs receiving metronidazole at doses ranging from 67 to 129 mg/kg of body weight per day, for 3 to 14 days, showed signs of acute neurological dysfunction severe generalized ataxia and vertical, positional nystagmus, usually preceded by anorexia and intermittent vomiting [118]. Increased levels of protein were noted in 2 of 3 dogs from which CSF was collected. Two dogs were euthanatized because of severe neurological dysfunction. Three dogs slowly improved and eventually recovered completely after several months. Axonal degeneration was seen in vestibular tracts of one dog, while bilateral leukomalacia was found in another dog near the radix of the vestibular nerve. It was concluded that currently recommended dosages of metronidazole for dogs were excessive, and a total daily dosage of 30 mg/kg was recommended [118]. In another report involving a 2 year old Plott Hound-cross dog (receiving metronidazole at 89.5 mg/kg/day for 5 weeks) with progressive ataxia, nystagmus and knuckling, who was disoriented, had intermittent excitatory episodes, consisting of paddling, muscle spasms and vocalization, with involuntary urination during defecation, neurological abnormalities were reversed within 2 weeks after discontinuation of metronidazole therapy [119]. Interestingly, in a recent report from Sweden, adverse CNS signs were associated mainly with metronidazole administration to Collies [120]. In one retrospective study involving 20 dogs with metronidazole toxicosis (ranging from 60 - 65 mg/kg over 37 - 45 days), recovery was enhanced by administration of diazepam (the average intravenous/oral

dosage was 0.43 mg/kg tid for 3 days) [212]. It was postulated that this positive effect might result from diazepam competitively displacing metronidazole from GABA receptors. In cats, receiving metronidazole from 58 to 222 mg/kg, daily, for up to 6 months, neurological abnormalities seen include disorientation, ataxia, seizures, and blindness [121,122]. The neurological signs in all cats resolved within days of initiating supportive therapy and withdrawal of the drug.

### Organophosphate/Carbamate Toxicity

Organophosphate and carbamate compounds are widely employed for control of external parasites in dogs and cats and for control of insects in the home and garden. Cats are relatively susceptible to acute toxicosis by the organophosphate compound chlorpyrifos [123]. Toxicosis may develop following ingestion of liquid concentrates or granules of these compounds or from excessive skin/hair coat dusting or painting [63]. Organophosphates and carbamates are acetylcholine esterase (ChE) enzyme inhibitors: -organophosphates are irreversible inhibitors of the enzyme, whereas carbamates are reversible inhibitors of ChE. This results in an accumulation of the neurotransmitter acetylcholine, causing:

- a. overstimulation of the parasympathetic nervous system and subsequent development of muscarinic signs, e.g., salivation, lacrimation, urination, and defecation (SLUD), as well as pronounced gastrointestinal sounds, bradycardia, and pupillary constriction,
- b. nicotinic signs associated with skeletal muscle stimulation, e.g., muscle fasciculations, tremors, twitching, spasms that may result in a stiff gait or rigid stance, and eventually weakness and paralysis, and
- c. variable involvement of the central nervous system due to central cholinergic overstimulation (anxiety, restlessness, hyperactivity, anorexia, and generalized seizures).

The role of various serum and liver esterases in the pathogenesis of acute organophosphate toxicosis remains to be determined [63]. Death from asphyxia may result from severe central respiratory depression, bronchial fluid accumulation and bronchoconstriction. Clinical signs occur usually within minutes or hours. It has been reported that toxicity by the organophosphate compound, fenthion (Spoton®, Prospot®) usually results in a predominance of nicotinic signs (with no muscarinic signs), including muscle tremors, muscle weakness (particularly the neck muscles), and collapse after exercise [124]. In experimental intoxication with dichlorvos, muscle hemorrhage and necrosis was noted and was believed to be secondary to continual muscle fasciculations/contractions and possibly to the metabolic disturbances (metabolic acidosis and tissue hypoxia) produced in muscle as a result of ChE inhibition [125]. The myopathy associated with organophosphate toxicosis seems to be associated with excessive entry of calcium ions into muscle cells [126]. In a clinical report, acute polymyopathy in a 7 year old German Shepherd dog was attributed to the muscular hypertonia, tremors and seizures which developed during the acute phase of carbamate poisoning [127]. After two days of generalized muscular rigidity, the dog adopted a characteristic fetal position thought to be explained by the imbalance between the injuries to the extensor and flexor muscles. The polymyopathy, the diagnosis of which was based on EMG findings, myoglobinuria, and elevated serum muscle enzymes (muscle biopsy was normal), resolved gradually over the course of a week. A delayed neurotoxicity may occur in cats days or weeks after minimal exposure to organophosphates. In an experimental study, cats developed clinical signs of delayed neurotoxicity 16 to 18 days after di-isopropylfluorophosphate injection [128]. A histologic survey of the central and peripheral nervous systems revealed that the topographic distribution of axonal degeneration was characteristic of a dying-back neuropathy. In teased-fiber preparations from the left recurrent laryngeal nerve, the axonal degeneration that was initially focal and nonterminal subsequently spread in a somatofugal direction to involve the entire distal axon. Nerve fiber varicosities and paranodal demyelination preceded the axonal degeneration. The varicosities were associated ultrastructurally with intra-axonal and/or intramyelinic vacuoles, along with accumulations of axonal agranular reticulum [129]. Neurotoxic esterase is considered to be the target enzyme in the production of organophosphorus-induced delayed neurotoxicity (OPIDN) [130,131]. Affected animals manifest signs of a **neuropathic syndrome**. Dogs appear to be relatively resistant to delayed neurotoxicity [132]. Clinical signs associated with carbamate toxicity are likely to be less severe and shorter in duration [63]. ChE activity in domestic animals has been recommended as a potential biomonitor for nerve agent and other organophosphate exposure [133]. In this regard, it should be noted that physostigmine is a reversible ChE inhibitor and has a short duration of action. It crosses the blood-brain barrier readily; hence, it is a centrally acting carbamate. Pretreatment with physostigmine rapidly improves the incapacitating effects of organophosphate intoxication in various animal species [134]. Physostigmine carbamylates to a portion of ChE enzyme and thus protects the enzyme from irreversible binding with organophosphate.

Diagnosis is suggested by historical data, clinical signs and response to therapy. Whole blood cholinesterase levels can be determined using several substrates, including acetyl-, butyryl- and propionylthiocholine [217]. Red blood cell ChE levels reduced by 25% or more will confirm exposure [11]. At post mortem examination, brain tissue submitted for ChE activity is the most definitive diagnostic measure available for lethal organophosphate toxicosis [123]. Atropine, a muscarinic cholinolytic agent, at a dosage of 0.2 to 0.4 mg/kg body weight, IV, slowly over 5 minutes, usually results in a dramatic

cessation of muscarinic signs within 3 to 5 minutes. Repeated administration of atropine, SC or IV, at lower dosages is often required, especially in cats. Atropine blocks the effects of accumulated acetylcholine at muscarinic parasympathetic nerve endings. However, it does not affect the skeletal muscle (nicotinic) signs. Repeated doses of atropine can be given using one-half the initial dose. Overatropinization can cause tachyarrhythmias, pyrexia, behavioral excitation and signs of delirium. Additionally, a ChE-reactivating oxime, such as pralidoxime chloride (2-PAM, Protopam Chloride) may be used to counter the nicotinic cholinergic signs. This compound acts by forming a relatively non-toxic complex with the organophosphate compound that can be excreted in urine, and also reactivates acetylcholine esterase. 2-PAM works best in the presence of atropine, the dose of which may be reduced when 2-PAM is used (e.g., 0.04 to 0.4 mg/kg once, or as needed). The dose of 2-PAM (given as a 10% solution) is 10 to 20 mg/kg for cats and 40 mg/kg for dogs, given IV slowly, or with fluids over a 30 minute period [11]. Signs of muscle weakness and fasciculations usually disappear within 30 minutes. If signs remain, repeat the dosage within an hour and then give every 8 hours, for 24 to 48 hours, or until recovery. Treatment with 2-PAM should begin within 24 to 48 hours and this agent may be especially beneficial in animals exposed to fenthion and chlorpyrifos with their slow rate of elimination [11]. The dose can be reduced in animals that are severely depressed, weak and anorectic one or more days after exposure. Oximes are of not benefit in treating carbamate toxicosis and may worsen the animal's condition. Orally administered activated charcoal in cats and dogs (0.5 to 4.0 gm/kg), in combination with a saline cathartic (e.g., 70% sorbitol), will help reduce absorption following ingestion of organophosphate/carbamate compounds. Seizures in cats and dogs may be controlled using diazepam (2.5 to 5.0 mg/kg IV as needed) or a barbiturate such as phenobarbital (10 to 20 mg/kg IV as needed). Supportive care is very important, especially in cats, and includes monitoring for hypo- and hyperthermia, oral or parenteral potassium supplementation if hypokalemia is detected, and parenteral fluid, electrolyte and nutritional support (e.g., hand-feeding, tube-feeding, or use of pharyngostomy tubes) [123]. Such care may extend over several weeks.

Diphenhydramine (Benadryl®) may be effective in treating organophosphate-induced neuromuscular weakness in dogs and cats, that is refractory to other forms of therapy [135,136]. Initial treatment should be initiated IV or IM (IM only in cats) at 4 mg/kg every 4 to 6 hours until clinical improvement occurs, followed by oral treatment at 4 mg/kg, tid. Diphenhydramine blocks the nicotinic and muscarinic effects of compounds such as fenthion (Spoton®). Experimental studies have shown that early and prolonged treatment using a high-dose regimen of methylprednisolone prevented the development of OPIDN in cats [137].

Variations in clinical presentations may occur with organophosphate compounds. In one report, two cats with chronic exposure (3 weeks) to chlorpyrifos (Dursban®), an organophosphate available as a soil insecticide and a parasiticide for use on cattle, presented with paraparesis, generalized hyperesthesia, anorexia, depressed postural reactions and bilaterally dilated pupils that were partially responsive to light stimulation [138]. It was considered that both cats lacked muscarinic signs but showed evidence of nicotinic and central nervous system stimulation. Serum ChE activity was low in both cats and electromyographic studies revealed presence of fibrillation potentials and high frequency discharges, especially in more distal muscles of the pelvic limbs. Administration of 2-PAM, 20 mg/kg, IV, bid, for 5 or 6 treatments, as well as atropine sulfate, 0.05 mg/kg, SC, every 6 hours for 2 days, resulted in complete clinical recovery. Interestingly, diazepam induced signs of acute organophosphate toxicity (miotic pupils, hypersalivation, generalized muscle fasciculations, and depression) in both cats - the mechanism of action was not determined.

### **Pemoline**

Extreme agitation, hyperactivity, and vomiting that began within 24 hours after ingestion of approximately 750 mg of pemoline, a CNS stimulant used in humans for treating attention deficit-hyperactivity disorder in adolescents, was reported in a 3 year old German Shorthaired Pointer [139]. The dog was tachycardic, hyper-responsive, pyreptic, disoriented, and had mydriasis. These signs were consistent with excessive stimulation of the CNS and sympathomimetic effects resulting from pemoline toxicosis. Plasma pemoline concentration was markedly elevated (32 hours after ingestion the plasma concentration was 368 µg/ml, compared with a therapeutic concentration of 1.7 to 7.0 µg/ml reported for children). Several sedatives were administered intravenously to alleviate clinical signs and to allow administration of activated charcoal and fluids. Clinical signs resolved approximately 72 hours after ingestion of pemoline.

### **Pyrethrin and Pyrethroid Insecticides**

These compounds are used as parasiticides and formulated for use in dogs and cats as shampoos and dips. Pyrethrins are natural insecticides while pyrethroids (e.g., permethrin and fenvalerate) are synthetic compounds and classified as type I (no alpha cyano-3-phenoxybenzyl group) or type II (with alpha cyano-3-phenoxybenzyl group) [2,140]. These insecticides are thought to interfere with sodium channels (type I pyrethroids and pyrethrins), enhance sodium ion conductance, and block post-synaptic GABA-A receptor-chloride ionophore complexes (type II pyrethroids). Cats may be more susceptible to pyrethrin/pyrethroid poisoning than dogs [11]. Signs of toxicosis may occur within hours of exposure (but may be delayed) and include tremors, salivation, ataxia, vomiting, depression, hyperexcitability, hyperactivity, seizures, dyspnea, and death

[2]. Treatment is symptomatic and supportive, including dermal decontamination, emesis induction within 1 hour (e.g., apomorphine at 0.03 mg/kg IV or 0.04 mg/kg IM), activated charcoal (2 g/kg, qid), magnesium sulfate or sodium sulfate (0.5 g/kg PO as a 10% solution in water), anticonvulsants, oxygenation (if necessary), and fluid therapy. The syndrome is generally reversible, with most animals recovering within 72 hours [33].

### **Strychnine Poisoning**

Strychnine is a rodenticide poison used for "control" of squirrels, gophers, rabbits and other wild carnivora [63]. Dogs, and infrequently cats, become poisoned when they eat strychnine baits, especially in rural areas, although dogs also may be poisoned maliciously in rural and urban areas [63,141-144]. In one report on 261 cases of strychnine poisoning in dogs in Canada [145], strychnine poisoning occurred more often in younger dogs, with 61% of the cases being in animals less than 2 years old. Large breeds of dogs and male dogs were affected more often. In this study, the German Shepherd was the most common breed of dog affected.

Strychnine acts at the brainstem and spinal cord level by stereochemically and competitively blocking the motor inhibitory neurotransmitter, glycine. Some supraspinal signs may also be associated with strychnine inhibition of gamma-aminobutyric acid (GABA). Clinical signs of poisoning are induced by uncontrolled impulses reaching skeletal muscles and are characterized by retraction of the corners of the mouth, drawing together of the ears, stiffness of muscles of the neck, chest and abdomen, stiffness of gait and assumption of a "sawhorse" stance followed by tonic extension of the limbs, opisthotonus, vocalization, and difficult respiration. Affected animals are hypersensitive to auditory, visual (e.g., bright light), and tactile stimuli [11]. Consciousness is not lost during initial "seizural" attacks. After several minutes, the attack(s) may subside only to be followed by further episodes. Eventually, the respiratory muscles may be unable to function. Apnea can lead to cerebral anoxia, loss of consciousness and death. The entire course may last from 30 minutes to 1 to 2 hours, if the animal is untreated. Atypical signs, including absence of seizures or tetanic spasms, and time course (e.g., 10 hours) have been reported in dogs [216].

A presumptive diagnosis is based on a history of ingestion and characteristic clinical signs. In one report, chemical analysis of tissues and ingesta containing strychnine indicated that the highest concentrations were in stomach contents, followed by the liver, and the kidney [145]. Vomitus and urine can also be screened. The dimethoxy derivative of strychnine, brucine (2,3-dimethoxystrychnidin-10-one), may be detected in serum [216]. Prognosis is guarded, depending on the amount of poison ingested and/or promptness of treatment. The main objectives of treatment are to keep the muscles relaxed and to prevent asphyxia. The drug of choice in dogs has been pentobarbital, at 30 mg/kg, IV (or via intraperitoneal or intrathoracic routes if the animal is difficult to manage or is having seizures). Thiobarbiturates, such as thiopental sodium or thiamylal sodium, given IV to effect, are recommended for cats. Muscle relaxants recommended include glyceryl guaiacolate ether given in an intravenous dose of 110 mg/kg in either a 5 or 33 1/3% solution [146]. This drug controls "seizures" for up to 60 minutes. It can be safely repeated as needed. Methocarbamol (Robaxin®) also can be used, at a dose of 150 mg/kg IV, and repeated as needed. Supportive treatment includes prompt gastric or enterogastric lavage using 1 to 2% tannic acid or 1:2000 potassium permanganate and enemas, followed by administration of activated charcoal. Forced diuresis with 5% mannitol in isotonic saline and acidification of urine with 150 mg/kg body weight of ammonium chloride PO, will enhance urinary elimination of strychnine.

If the animal survives 24 hours, prognosis for complete recovery is very good. The clinical signs and necropsy findings closely resemble plastic explosive type 4 (PE4 containing cyclonite) toxicity [147]. Roquefortine (a diketopiperazine alkaloidal tremorgenic mycotoxin) and strychnine poisoning may be difficult to differentiate clinically [148].

### **Tetanus**

Tetanus is a bacterial disease caused by *Clostridium tetani* that can affect all domestic animals and people. Disease occurs as a result of localization of tetanus spores in an anaerobic environment, such as a necrotic wound with suppuration, with conversion to a vegetative, toxin-producing form. Infection most frequently occurs following an injury, but may also develop after surgical procedures, such as ovariohysterectomy [149-152]. Organisms produce the exotoxin tetanospasmin within 4 to 8 hours, which travels via peripheral nerves (alpha motor neurons) to the CNS [153]. A trans-synaptic migration of tetanus toxin occurs in spinal cord motor neurons. Small amounts of toxin may be spread hematogenously to the CNS. Tetanus neurotoxin appears to prevent synaptic vesicles from fusing with the cell membrane and prevents the release of neurotransmitters [154,155]. It is active at the neuromuscular junction, autonomic terminals, and in inhibitory neurons in the CNS, with the central effects usually predominating the clinical picture. Toxin causes disinhibition on gray matter gangliosides [106] and binds the release of inhibitory neurotransmitters from interneurons (glycine) and from descending upper motor neuron pathways (gamma aminobutyric acid) resulting in release of spinal cord and brainstem motor neurons from inhibition and subsequent hyperexcitability [156,157]. In people, at high concentrations, tetanus toxin acts like botulism toxin in that it inhibits the release of acetylcholine at cholinergic synapses [106].

Considerable species differences exist in susceptibility to tetanus. The dog is much less susceptible than the horse, and



tetanus is seen less commonly in cats than in dogs. Clinical signs usually are observed within 4 to 12 days of infection [158-162], although extensor rigidity and ptialism were observed in one dog 3 weeks after a routine ovariohysterectomy [151]. Frequently seen signs include stiffness of gait with extensor rigidity in all limbs, dyspnea, and spasms of the masticatory and pharyngeal muscles resulting in trismus and dysphagia. The tail may be elevated, facial muscles may be contracted to give a sneering expression ("risus sardonicus") with wrinkling of the forehead and puckering of the skin around the eyes, and the third eyelid may be protruded. Earflaps are usually held in an erect fashion, although low carriage has been noted early in the condition in some animals [163]. Animals may assume a "sawhorse" stance. In severe disease, the animal may be recumbent and opisthotonic. Affected animals are hypersensitive to external stimuli and reflex muscle spasms may occur. Autonomic involvement, such as bradyarrhythmias [164], or tachycardia/tachyarrhythmias [165], may result from increased vagal tone or adrenergic stimulation, respectively. Death results from respiratory failure.

Localized tetanus may also be seen in dogs and cats with a localized limb injury and is usually characterized by stiffness in one limb before gradually spreading to involve the opposite limb and eventually, the entire body [162]. Tetanus in cats and dogs may remain localized to one of the thoracic limbs, which is held in rigid extension and caudally deflected (elbow extension and carpal flexion or extension) due to continuous involuntary muscle spasms [166,167]. Intermittent spasms may be superimposed upon the tonic rigidity. In one of the affected cats, the neck became twisted to the side [166]. The affected limb does not appear to be painful. Localization to both thoracic limbs, along with mild trismus and forehead wrinkling, has been seen in one affected cat [213].

Potential complications include bony fractures from spasms or seizures, dyspnea from laryngeal spasms, inhalation pneumonia from dysphagia, and decubital ulcers. Urinary and fecal retention may be associated with anal and urethral sphincter/bladder spasms. In such instances, urinary stasis may lead to hemorrhagic, purulent cystitis [168,169]. Gastric and intestinal bloating may also occur [169]. Transient megaesophagus and/or hiatal hernia have been reported in association with gastro-esophageal reflux and regurgitation [170,171]. It has been reported that the hiatal hernia developed approximately 2 weeks after the beginning of clinical signs of tetanus [171,172]. Tetanus has been reported as a complication in dogs during parturition [173] and pregnancy [174].

To my knowledge, structural changes in the CNS or PNS have not been reported in dogs or cats. In people, degenerative changes may be found in the cerebral cortex and brainstem, along with hemorrhage, demyelination, and gliosis in chronic cases [106]. Diagnosis of the severe form of tetanus is largely based on characteristic clinical data. Mild forms of the disease may be difficult to diagnose since there are no specific ancillary aids available. There is a lack of the usually observed electrical silence following needle insertion in electromyographic studies. Nerve conduction studies are normal.

Megaesophagus and/or hiatal hernia in animals with tetanus can be diagnosed radiographically [170].

Since tetanus is often mild or localized in dogs and cats, prognosis is usually favorable with treatment, which consists of penicillin G (e.g., 20,000 to 100,000 units/kg, qid, IV, as the aqueous potassium or sodium salt or IM, as the procaine salt), and immediate administration of tetanus antitoxin (TAT) (e.g., 100 to 1,000 IU/kg IV) [160]. Antibiotic therapy is aimed at any remaining vegetative *C. tetani* organisms in the wound, while the antitoxin is given to neutralize any toxin that remains unbound to the CNS. A test dose (e.g., 0.1 - 0.2 ml) of TAT can be given SC 20 minutes prior to the intravenous dosage and the animal observed for any anaphylactic reaction. If a wound is present, radical debridement and excision of all infected or necrotic-appearing tissue should be performed, along with peroxide irrigation to reverse the anaerobic state, and local intramuscular instillation of 1,000 units of TAT and 1,000,000 units of procaine penicillin G, in and around the wound site. Metronidazole is also effective (at 10 mg/kg, PO, tid, in dogs, and at 250 mg, PO, sid or bid, in cats). Antibiotic therapy should be continued for at least 10 days. Chlorpromazine (e.g., 0.5 - 2.0 mg/kg IM, IV, or PO, bid or tid, in dogs and cats) and pentobarbital (e.g., 3 - 15 mg/kg, IV or IM, every 2 - 3 hours, in dogs and cats) can be used to control reflex spasms and convulsions. Tracheostomy may be needed if laryngeal spasms are severe [22]. Esophagostomy or gastrostomy tubes or gastric tube feeding may be necessary if trismus prevents feeding or if megaesophagus and/or hiatal hernia are present along with gastro-esophageal reflux and regurgitation [22,171]. Prompt treatment usually results in a favorable prognosis [150,161,171], although complete remission of clinical signs in dogs and cats with generalized or localized tetanus may take 3 to 5 months [166]. A guarded to poor prognosis has also been reported in severely affected animals [22,169].

Megaesophagus and/or hiatal hernia tend to resolve with resolution of the tetanus [170], although, in one report, all dogs with this complication that were fed normally, died [171]. Nursing care is important to monitor nutritional and fluid balance.

## **Thallium**

Thallium poisoning, from ingestion of thallium-containing rodenticides, may produce vomiting, bloody diarrhea, salivation, anorexia, depression, paralysis, trembling, dyspnea, and death in 3 - 5 days [175]. Degenerative changes have been observed in peripheral nerves [176]. Today, thallium toxicosis is relatively rare as rodenticides containing it are banned in the USA. Thallium toxicosis can be confirmed by detection of thallium in the urine, using colorimetric analysis. Treatment involves use of diphenylthiocarbazone (dithizone) to increase the rate of thallium excretion from the body, administration of antibiotics, fluid therapy, warm-water enemas, and oral administration of activated charcoal slurries [177,178].

## Tick Paralysis

This is a flaccid, afebrile ascending motor paralysis in animals and people, produced by a neurotoxin generated by some but not all strains of certain species of ticks. Not all infested animals become paralyzed. Cats in the U.S. appear to be relatively resistant to tick paralysis, although signs of paralysis have been reported [179]. In North America, the common wood tick, *Dermacentor variabilis*, and *Dermacentor andersoni* (the Rocky Mountain wood tick) are incriminated most often. In Australia, especially along the east coast, *Ixodes holocyclus* is the most important species. Other species that occasionally cause paralysis are *Ixodes cornuatus* and *Ixodes hirsti*. *Ixodes scapularis*, the principal vector of the agent of Lyme disease (*Borrelia burgdorferi*) in the Northeast, Midwest, and Southeast of the United States, can also cause tick paralysis in dogs [180]. This tick is also a primary vector of the agent of human and rodent babesiosis. *Ixodes pacificus* has also been incriminated in dogs in the Grass Valley area (Nevada Co.) of northern California [181,182]. In Australia, *Ixodes holocyclus* is the vector for Lyme disease and spotted fever, caused by *Rickettsia australis* [183]. There is circumstantial evidence that some dogs bitten by *Ixodes holocyclus* develop signs of chronic illness similar to Lyme disease [183]. With tick paralysis, adult ticks, especially females, produce a salivary neurotoxin that circulates in the host animal and interferes with acetylcholine liberation at the neuromuscular junction and/or impulse propagation along motor axon terminals. In Australia, heavy infestations with nymphs or larvae may result in paralysis [184].

Onset of clinical signs is gradual, paralysis first becoming evident as an incoordination in the pelvic limbs, resulting in an unsteady gait. Altered voice, cough, and dysphagia can be early signs. Dogs become recumbent in 24 to 72 hours. Reflexes are lost but sensation is preserved. Jaw muscle weakness and facial paresis may be present. Death may occur within several days from respiratory paralysis. Electromyographic studies reveal absence of spontaneous potentials and lack of motor unit action potentials. No muscle response follows direct nerve stimulation. Motor and sensory nerve conduction velocity may be slower than normal. Prognosis is usually good with recovery occurring in 1 to 3 days following tick removal or dipping the animal in an insecticide solution. Administration of a systemic insecticide (e.g., cythioate, 3 - 6 mg/kg, PO) can be used to kill any hidden ticks on dogs. Assisted ventilation is necessary in cases with respiratory failure.

In Australia, tick paralysis is a far more serious and life-threatening condition [185-188]. Central effects include sympathetic stimulation that can produce peripheral vasoconstriction, arterial hypertension, increased pulmonary capillary hydrostatic pressure, pulmonary congestion and edema, tachyarrhythmias, and pupillary dilation. Respiratory embarrassment, in addition to diaphragmatic and intercostal paralysis, may stem from intoxication of medullary respiratory centers.

Furthermore, hypoxia, hypercarbia, and respiratory acidosis may accompany respiratory failure. Clinical signs usually begin with pelvic limb weakness that progresses to paralysis within a few hours. Ascending paralysis soon involves the forelimbs. Mydriatic pupils are poorly or unresponsive to light. Other signs may include voice change, depressed gag reflex, megaesophagus, salivation, regurgitation and/or vomiting, labored breathing, dyspnea, and cyanosis. Death occurs within 1 to 2 days if dogs are untreated. Similar signs are seen in cats with tick paralysis due to *Ixodes* sp. Focal forms of tick paralysis, such as asymmetrical facial paralysis and anisocoria, have been seen in some dogs, while others may only present with vomiting and loss of voice [184,189]. Short-term, acquired humoral immunity develops in animals following exposure to the toxin. Treatment involves removal of ticks, neutralization of circulating toxins, and supportive therapy. Painting ticks with pyrethroids and leaving the tick to die in situ may reduce mortality and anaphylactoid reactions in sensitized patients [190]. Intravenous polyclonal hyperimmune serum (e.g., 0.5 - 1.0 ml/kg, IV) is suggested for dogs. For affected cats, administration of hydrocortisone (30 mg/kg, IV) followed by slow intravenous injection of serum (5 - 10 ml) is recommended [184]. This antiserum treatment is expensive and effective only in the early stages of paralysis [191]. In a recent survey from Australia, adverse reactions following tick antitoxin serum were reported in 3% of dogs and 6% of cats, with only a small percentage of these reactions associated with anaphylaxis [192]. The majority of adverse reactions were attributed to the Bezold-Jarisch reflex, a vagally mediated reflex initiated by chemical stimulation of cardiac receptors in the posterior wall of the left ventricle. Bradycardia, hypotension, reduction in total peripheral resistance and a slight reduction in myocardial contractility occurs with activation of these receptors [192]. A 1:1,000 solution of epinephrine should be available if animals show signs of anaphylaxis. Recommended dosage is 0.01 ml/kg IV or IM up to a maximum of 0.2 - 0.5 ml; repeat every 15 to 20 minutes if needed [192]. Due to the cholinergic nature of the Bezold-Jarisch reflex, atropine (at 0.1 - 0.2 mg/kg IV) will attenuate or abolish its clinical manifestations. A combination of phenoxybenzamine hydrochloride (e.g., 1 mg/kg as a 0.1% solution, given IV, over 15 minutes, every 12 to 24 hours) and acepromazine (0.05 - 0.10 mg/kg, IV, every 6 to 12 hours) produces sedation, helps relieve the respiratory distress, and resolves any cardiac arrhythmias [184,193]. Phenoxybenzamine hydrochloride, an alpha-adrenergic blocking drug, is thought to attenuate the arterial hypertension [188,193]. Some severely affected animals may require supplemental oxygen or intermittent positive pressure ventilation. Affected animals should be kept in a quiet, air-conditioned environment [184]. Food and water should be withheld until animals are walking and have not vomited for 24 hours. Weekly dips, use of collars impregnated with insecticide (e.g. permethrin) [190], or regular use of the organophosphate agent cythioate (3 mg/kg, PO, every 3 days) will help prevent tick paralysis in Australia. In a recent report from Australia, a correlation was noted between use of Lufenuron (a member of the benzoylphenylurea group of compounds used in dogs and cats for flea control) and lack of

envenomation/paralysis caused by *Ixodes holocyclus* [194]. Despite treatment, prognosis can be guarded with this form of tick paralysis. In a recent survey of 577 dogs affected by tick paralysis, younger dogs were more likely to survive, and respiratory and gait scores reflected disease severity and were good prognostic indicators, in that dogs with mild disease recovered more quickly, whereas those with severe disease that received an additional dose of tick antitoxin serum were significantly less likely to survive [195].

Sensitive biological assays of toxin/antitoxin potency have been developed to assist in research on characterization of salivary toxins of the Australian paralysis tick *Ixodes holocyclus* and on immunity to tick paralysis [196]. The aim of current research is to develop a recombinant veterinary vaccine based on the tick neurotoxin peptide sequence. A successful vaccine would provide cost-effective, long-term protective immunity against tick-induced paralysis [191].

### **Toad Toxicity**

This condition occurs in animals that bite or mouth various species of toads that contain bufotoxins within their parotid glands. Toxic species include the Colorado River toad (*Bufo alvarius*) and the marine toad (*Bufo marinus*). Toxicity is common in dogs in Florida and in Australia, especially in Queensland, where there is a seasonal incidence, primarily from September/October through April [197]. In one report from Florida, most dogs were treated during the spring and summer [198]. Toads tend to breed during the warmer and wetter months and hibernate during the colder and dryer months. Terrier breeds are commonly affected associated with their inquisitive nature and their tendencies to pursue hopping toads [197]. Cats are infrequently reported. Clinical signs develop within minutes of mouthing the toad and include profuse salivation, head shaking, ataxia, vomiting, polypnea, hemorrhagic diarrhea, and seizures in severe cases. Some dogs are presented in status epilepticus. Other neurological signs may include stupor, nystagmus, extensor rigidity, and opisthotonus [198]. Common EKG findings with *Bufo Marinus* include sinus arrhythmia, tachycardia, and occasionally ventricular fibrillation [198,199]. Abnormal cardiac depolarization and arrhythmias have been experimentally shown using resibufogenin and bufalin from toad venom [200]. Bufalin, from the *Bufo marinus* toad, is structurally and functionally similar to digitalis glycosides [201]. Death may occur within 30 minutes. Treatment involves washing the buccal mucosa with a swab or hose to dilute the toxin, intravenous diazepam (e.g., 0.25 to 1 mg/kg, IV), intravenous atropine (e.g., 0.04 mg/kg) and, if required, intravenous pentobarbital (e.g., 2.5 to 7.5 mg/kg, IV). Propranolol (e.g., 1.5 to 5.0 mg/kg, IV, rapidly, followed by a repeat dose in 20 minutes, for dogs and cats) is recommended, especially if ventricular fibrillation develops [199]. Prognosis will depend on the potency of the toxin, quantity absorbed, and size of the patient. It is usually favorable when animals are treated promptly [198], but may be guarded once seizures are seen [197].

### **Toluene/Dichlorophen**

Toluene/dichlorophen anthelmintics (effective against ascarids, hookworms, and some tapeworms of dogs and cats) may cause adverse effects in healthy cats and dogs following oral administration of less than 1.5 times the recommended product dose [202]. Clinical signs usually are observed within 6 hours of dosing and include ataxia, aberrant behavior, mydriasis, vomiting, depression, muscle tremor, and hypersalivation. In this report, the four most common products associated with toxicosis in cats were Daltrek Tri-Wormer, De-Vos Control III Worm Caps, Zema Pulvex Multi-Purpose Worm Caps, and Vermiplex. In dogs, commonly involved products were Happy Jack's Trivermicide Worm Capsule, Farnam Triple Wormer, Zema Pulvex Multi-Purpose Worm Caps, Anchor Canine Wormer, and Performer Brand Dog Wormer. In most cases, clinical signs disappear within a few hours to a day with general supportive care.

### **Tricyclic Antidepressants**

Tricyclic antidepressants (TCAs), a class of psychotherapeutic medications, are widely prescribed for human patients, thereby increasing the potential for accidental oral ingestion by companion animals [203]. Animals ingesting TCA in an amount exceeding 15 mg/kg are in grave danger. TCAs block re-uptake of biogenic amines (e.g., epinephrine), have anticholinergic (atropine-like) effects, and quinidine-like action on the cardiovascular system. Clinical signs in animals include hyperexcitement and vomiting followed by ataxia, lethargy, and muscular tremors. Bradycardia and cardiac arrhythmias should be anticipated in the later stages of the TCA toxic syndrome [203]. In a review of over 450 cases reported to the Illinois Animal Poison Information Center between 1985 and 1989, more than 7% of affected animals eventually died [203]. Initial therapy includes intubation, oxygen administration, enterogastric lavage, and activated charcoal via a stomach tube. Animals in a hyperactive state should receive diazepam (0.5 mg/kg IV or IM, repeated as needed, every 10 minutes for three doses), followed by activated charcoal (2 gm/kg, every 3 - 4 hours, PO) and a suitable cathartic, such as sorbitol (0.5 gm/kg, PO) or sodium sulfate (Glauber's salts) at 0.25 gm/kg, PO. Magnesium sulfate (Epsom salts) is not recommended because of the TCS-induced decrease in GI motility. Intravenous sodium bicarbonate at 2 - 3 mEq/kg, over 15 - 30 minutes, should be given if acidosis, hypotension, tachycardia, or other cardiac abnormalities are noted. Blood pH should be maintained above 7.5.

## **Vincristine**

Vincristine is a vinca alkaloid widely utilized in cancer chemotherapy. Its major clinical limitation is due to a drug induced sensory-motor neuropathy, the pathogenesis of which is poorly understood. In cats with experimental vincristine neuropathy, major pathological lesions were focal axonal swellings (giant axon formations) due to malaligned accumulations of neurofilaments and secondary paranodal demyelination [204]. These were primarily confined to the proximal portions of the peripheral nerves. Wallerian degeneration involved a small number of nerve fibers in the distal regions. Muscle spindles were affected and motor nerve conduction velocities were reduced by 30% [205]. We reported a vincristine-induced peripheral neuropathy in a 12 year old, female, Golden Retriever that received 16 weekly doses of vincristine (0.5 mg/m<sup>2</sup>) as part of a regimen for treatment of mycosis fungoides [206]. The dog was presented for sudden onset of a shuffling pelvic limb gait, intermittent collapse, and difficulty negotiating turns and stairs. Neurological examination revealed mild ataxia in the pelvic limbs, depressed pelvic limb postural reactions, and depressed patellar and pelvic limb withdrawal reflexes. Electromyographic testing revealed fibrillation potentials and positive sharp waves consistent with denervation. Sciatic motor nerve conduction velocity was decreased. Evoked muscle potentials were polyphasic and had reduced amplitude and prolonged duration. Severe nerve fiber degeneration, nerve fiber loss, and endoneurial fibrosis were seen in a nerve biopsy sample. The neuropathy improved after vincristine was discontinued. Results of a repeat nerve biopsy taken 10 weeks after cessation of vincristine administration showed fewer degenerating nerve fibers and presence of demyelination-remyelination. The dog appeared neurologically normal at this time. In people, vincristine-induced neurotoxicity is aggravated by itraconazole [207,208].

## **Zolpidem**

Zolpidem is a nonbenzodiazepine hypnotic and sedative of the imidazopyridine class used for treating short-term insomnia in humans. The drug increases the frequency of chloride channel opening and inhibits neuronal excitation. A retrospective review of zolpidem ingestion in 33 dogs that were reported to the ASPCA Animal Poison Control Center between January 1998 and July 2000 revealed that ingested dosages ranged from 0.24 to 21 mg/kg [211]. Clinical signs reported included ataxia, hyperactivity, vomiting, lethargy, panting, disorientation, nonspecific behavior disorder, hypersalivation, tachycardia, tremors, apprehension, vocalization, weakness, and hyperesthesia. In most instances, clinical signs developed within 1 hour and typically resolved within 12 hours. Treatment includes induction of emesis within the first 1 to 2 hours (or gastric lavage), use of activated charcoal in conjunction with a cathartic, such as sorbitol, and fluid administration. Note that supportive treatment (e.g., phenothiazines or barbiturates) may be used to treat signs of stimulation and hyperactivity; however, the use of diazepam or other benzodiazepines should be avoided.

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## Nutritional Disorders ( 22-Oct-2002 )

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Several nutritional disorders involving selective deficiency or excess of one or more essential dietary ingredients may have neurological implications in dogs and cats. In most instances, these essential dietary ingredients involve vitamins. Complications may arise in precise diagnosis in some cases due to possible multiple deficiencies co-existing in patients in association with conditions such as malnutrition and malabsorption disorders.

The following nutritional disorders involving the CNS will be discussed:

- Cobalamin Deficiency
- Hypervitaminosis A
- Nutritional Secondary Hyperparathyroidism
- Thiamine Deficiency
- Vitamin E Deficiency

### **Cobalamin Deficiency**

Cobalamin (vitamin B12) is an essential cofactor for two enzyme systems (a) folate-dependent methionine synthetase activity, which is required for nucleic acid synthesis and for normal development, growth, and hematopoiesis. This cytosolic enzyme catalyzes the conversion of homocysteine and methyltetrahydrofolate to produce methionine and tetrahydrofolate; methionine is further metabolized to S-adenosylmethionine, a substrate necessary for methylation of myelin sheath proteins and phospholipids. (b) Methylmalonyl CoA mutase, which uses adenosylcobalamin for the degradation of propionate through methylmalonyl CoA to succinate in mitochondria [1,2]. Selective cobalamin malabsorption associated with chronic inappetence, lethargy, cachexia, and failure to thrive has been reported in Giant Schnauzer puppies and is inherited as an autosomal recessive trait [3,4]. This disorder is characterized by methylmalonic aciduria, homocysteinemia, and low serum levels of cobalamin, and due to a selective defect of cobalamin absorption at the level of the ileal enterocyte [4]. The spontaneous disorder is believed to be analogous to Imerslund-Grasbeck syndrome in humans [4]. Hereditary cobalamin deficiency has also been reported in Border Collie puppies [5]. Acquired cobalamin deficiency may occur in older dogs and cats in association with malnutrition, malabsorption, exocrine pancreatic insufficiency, or bacterial overgrowth of the small intestine [6-13]. A condition similar to the inherited disorder has been recently described in a 6 month old beagle presented with a three-month history of failure to gain weight, lethargy, intermittent vomiting, and seizures [14]. Laboratory test results of low serum cobalamin concentrations, anemia, leucopenia, and methylmalonic aciduria while the dog was receiving a balanced commercial canine diet were suggestive of a congenital selective malabsorption of cobalamin. Treatment with repeated injections of parenteral cyanocobalamin at 50 µg/kg every two weeks corrected the cobalamin-deficient state and reversed all the clinical abnormalities. The pathogenesis of the neurological dysfunction in this dog remains unclear, although cobalamin is converted to adenosyl or methyl coenzymes that are necessary for normal neural metabolism [15].

A progressive encephalomyelopathy has been reported in a 12 week old Labrador Retriever with a variety of signs including stiffness and ataxia that progressed to tetraparesis, persistent turning of the neck/body to the right, changing nystagmus, decreased menace response, anisocoria, decreased oculocephalic reflex, ventrolateral strabismus, diminished gag reflex, and apparent dysphonia [69]. Gross changes revealed enlargement of the lateral, third, and fourth ventricles of the brain and white and grey matter atrophy. Syringomyelia and hydromyelia of the central canal into the dorsal funiculus of the spinal cord extended from the cervical intumescence to the lumbar intumescence. Significant biochemical abnormalities included methylmalonic and malonic aciduria, mild lactic and pyruvic aciduria. Disordered cobalamin metabolism was suspected, although serum cobalamin levels were normal. Neither ketoacidosis nor hyperammonemia were present. The condition was considered to represent an inborn error of metabolism resulting in abnormal organic acid accumulation (accumulation of

citric acid cycle intermediates including succinic, aconitic, and fumaric acids, and evidence of abnormal fatty acid oxidation, were also noted), with similarities to methylmalonic acidemia in neonatal humans, an autosomal recessive disorder caused by defective activity of methylmalonyl CoA mutase or by defective intramitochondrial processing of vitamin B12 [70]. Many of the human patients respond to large doses of vitamin B12. Interestingly, an 8 week course of L-carnitine (1000 mg/day), vitamin B12 (0.5 mg/day), and a protein restricted diet resulted in marked improvement in the organic acid values of this dog, but no clinical improvement.

Malonic aciduria without elevated methylmalonic acid has been reported in a family of Maltese dogs with signs of episodic seizures and stupor (the dog described was 3 years of age), along with hypoglycemia, acidosis and ketonuria [71]. Treatment with frequent feedings of a low-fat diet high in medium-chain triglycerides successfully reversed signs and resolved the malonic aciduria.

In people, vitamin B12 deficiency results in spongy demyelination of the posterior (dorsal) columns and corticospinal tracts (once termed "subacute combined degeneration of the spinal cord"), and white matter of the cerebral hemispheres [16]. Peripheral neuropathy has also been reported that is usually axonal in nature [17], or less often, demyelinating [18]. Results of experimental studies suggest the pathogenesis of the myelopathy associated with vitamin B12 deficiency is related to interference with the methylation reactions in the central nervous system (CNS) that are processed by S-adenosylmethionine, which is controlled by its product, S-adenosylhomocysteine [19,20]. As a consequence, there may be inhibition of methyltransferases involved in the synthesis of myelin. Neuropathological studies on vitamin B12 deficiency are sparse in small animals. However, a degenerative spinal myelinopathy with similarities to subacute combined degeneration of the spinal cord in people has been reported in dogs fed a diet composed mainly of ruminant stomachs (see hound ataxia) [21]. The disorder was associated with methionine deficiency and altered methionine synthetase activity. Peripheral nerves appeared normal. The condition disappeared when the diet was changed to one containing a high proportion of meat. A possible relationship between degenerative myelopathy (especially in German Shepherds) and vitamin B12 deficiency has been studied but no consistent abnormalities in serum cobalamin levels could be shown [22]. Furthermore, parenteral cobalamin was ineffective in preventing progression of the neurological signs (see [23]).

### **Hypervitaminosis A**

Hypervitaminosis A or deforming cervical spondylosis is a crippling degenerative and proliferative bony disorder typically affecting the vertebral column and various long bones in cats fed whole liver (usually beef or sheep, but also pig and chicken) diets [24-29]. The disorder is caused by excessive intake of vitamin A in the liver. Excessive intake of vitamin A supplements can also produce the disease. In serum, vitamin A is transported in a retinol binding protein and as retinylesters (retinylpalmitate, -stearate) in very-low and low-density lipoproteins [30]. Chronic hypervitaminosis A in cats is characterized by new bone formation or exostoses, principally involving cervical vertebrae, and in the region of tendon, ligament, and joint capsule attachments [26]. Early changes involve periarticular cartilaginous and osseous hyperplasia of cervical vertebrae, especially the first three diarthrodial joints, without changes in the articular hyaline cartilage or other signs of inflammation [26]. These lesions tend to coalesce, overgrow joints, and cause complete bony ankylosis [25,31]. Cartilaginous epiphyseal growth plates are seriously disrupted in kittens [32]. In chronic cases, all cervical and cranial thoracic vertebrae may become involved, as well as sternbrae, periarticular regions of long bones and ribs. Nerve roots are often damaged secondary to exostoses encroaching on intervertebral foramina. Histopathological changes include subperiosteal proliferation of new woven bone around joints of affected vertebrae and proliferation of cartilage from the margins of the articular hyaline cartilage. There is erosion of adjacent cortical and cancellous bone and fibrous replacement of the myeloid marrow [25,31]. Periosteal proliferation may involve the tendinous insertions of muscle on the vertebrae and extend into surrounding muscle causing replacement and atrophy of the muscle fibers. In a study using back-scattered scanning electron microscopy [33], the more recently formed areas of bony proliferation were composed mainly of chondroid tissue surrounded by different degrees of woven bone. As the bony reaction continued, trabecular remodeling occurred leading to progressive substitution of chondroid tissue by woven bone surrounded by apposition of lamellar bone. In this study, there was no evidence of calcified cartilage present. In animals with extensive involvement of the spinal nerve roots, the spinal cord may show atrophy with disappearance of neurons and fibers, especially in the dorsal horns of the gray matter [25].

The underlying pathophysiologic mechanisms are not fully understood, but vitamin A toxicosis does appear to induce bone lesions via a direct effect on skeletal tissue. In young animals, toxicosis results in suppression of both chondrocytic and osteoblastic activity, leading to growth retardation and thinning of cortices. A high intake of vitamin A is necessary for several months or years before cervical exostoses develop, although experimental studies in kittens indicate that radiographic changes in the cervical spine can be detected as early as 15 weeks after beginning a diet rich in vitamin A [26]. After 24 weeks on the diet, the cervical spine from the occiput to C6 became completely rigid. Trauma may be a contributing factor in the pathogenesis due to constant movement of the neck in coat cleaning [26]. It seems that an individual predisposition to disturbances of vitamin A metabolism may be an important factor in the pathogenesis of the disease [34]. There are reports of

some cats having no symptoms while others in the household develop typical lesions [35].

Clinical signs usually occur in adult cats (e.g., 2 to 10 years of age) of either sex and in any breed [31,35-37]. Affected animals may be depressed, walk with pelvic limbs flexed, and may show lameness of one or both thoracic limbs associated with periarticular exostoses around the elbow joints, which, in chronic cases, are typically fixed in a flexed position. There may be ankylosis of the shoulder and carpal joints. Palpable exostoses of the forelimb distal to the elbow or of other regions of the skeleton are relatively uncommon [25]. Cats frequently assume a characteristic rabbit or kangaroo-like sitting posture. The head may be held in a ventroflexed position and there may be scoliosis of the cervical spine, which is frequently palpably rigid. The atlantoaxial joint is often fused, thus preventing any head-neck movement. Manipulation of the neck may be painful. Neurogenic muscle atrophy and signs of cervical hyperesthesia can result from spinal nerves compressed by the bony proliferation. Cutaneous hyperesthesia may be present over the shoulder and neck regions. Affected cats often have an unkempt coat because of inability to groom themselves. Affected cats typically have a fixed stare, presumably associated with reduced movement of the eyeballs caused by the head-neck rigidity [25]. Some animals have a voice change, probably related to proliferative exostoses that compress laryngeal structures (e.g., larynx, laryngeal muscles, and nerves). Some cats may show aggressiveness when handled [31,35]. Cats with advanced disease tend to become emaciated. In 6 to 8 week-old kittens fed raw sheep liver, severe retardation of skeletal growth was accompanied by delayed eruption, retention, and displacement of the incisor teeth with diffuse hypercementosis of the roots [38].

Radiographic studies reveal extensive new bone formation and variable autolysis of cervical and rostral thoracic, and sometimes, lumbar vertebrae [25,39]. In some cats, the skull and the cervical and first few thoracic vertebrae can be rigidly fused [25,40]. Periosteal exostoses can be seen involving multiple long bone articulations, especially in elbow and shoulder joints, and also ribs (in the region of vertebral articulation), sternbrae (showing irregular bony overgrowth, replacement and deformation of sternbrae with ankylosis of sternbral articulations), pelvic girdle, and hip joints. Curiously, there have been a few instances in which exostoses involving the pelvic girdle and hip joint were the major skeletal changes, without involvement of the cervical spine or forelimbs [25,33]. Rarely, affected cats showing typical clinical signs have no radiographic abnormalities in the cervical spine [40]. Vitamin A serum levels are elevated, but other hematologic and blood chemistries are usually normal, including alkaline phosphatase activity, serum calcium, and blood inorganic phosphate levels [25,29,37]. Vitamin A concentration is very high in liver and kidney [31,32] and there is extensive lipoid infiltration of the spleen [26], and fatty changes in the liver have been observed occasionally [29].

Prognosis of chronically affected cats is guarded to poor. Change in diet may halt further new bone formation and exostoses; however resolution of radiographic changes and clinical signs is unlikely, although some remodeling of bone may occur over a long period. Epiphyseal damage is irreversible. Nevertheless, encouraging improvement in signs has been noted in some cats following removal of liver from the diet [35,41] ( along with use of analgesic drugs, e.g., phenylbutazone, 13 mg PO, bid [37]. Cats have been treated with higher doses of phenylbutazone (12 - 16 mg/kg PO bid) for over a year without any toxic side-effects noted [25]. Rarely, temporary or permanent recovery may occur spontaneously [34]. Note that liver is highly palatable to cats and a change to another diet may be met with resistance [41].

The particular susceptibility of cats to hypervitaminosis A is difficult to explain. Spontaneous hypervitaminosis is rare in dogs but it has been experimentally induced in mixed Labrador Retriever pups [42]. Clinical signs were loss of body weight, dullness, emaciation, roughened coat, pain in limb joints, and retarded growth. Radiographic findings included reduced length and thickness of long bones, with osteophyte formation, periosteal reactions, and premature closure of epiphyses. No vertebral involvement was reported.

### **Nutritional Secondary Hyperparathyroidism**

Once this condition was relatively common in small animals but is now infrequent with the advent of commercially available balanced pet foods. The cause of nutritional secondary hyperparathyroidism (NSH) is chronic dietary calcium deficiency which leads to increased serum levels of parathormone, and accelerated bone resorption. Neurological signs most often relate to spinal fractures associated with severe osteopenia (decreased calcification or density of bone) associated with increased mobilization of calcium from bone. In a recent report of NSH in cats, seizures were a common reason for presentation [43]. Additional information on NSH is found in the section on hypocalcemia.

### **Thiamine Deficiency**

Thiamine or vitamin B1 deficiency (also called Chastek paralysis) occurs sporadically in dogs and cats if their commercial rations are naturally low in thiamine [44-47], or if their food (e.g., liver-beef diets in cats and mutton or mutton-beef in dogs) is overcooked prior to feeding or in processing of canned foods [44,48]. Sufficient quantities of thiamine to meet the requirements of dogs and cats are usually found in fresh meat [49]. Thiamine and thiamine pyrophosphate are thermolabile and destruction by heat (e.g. temperatures over 100°C) increases from a slight amount at pH 3.0 to a considerable degree at pH 7.0 [48,50]. In cats especially, thiamine deficiency may occur with an all-fish diet, since viscera of many freshwater and saltwater fish contain thiaminase [50]. Storage may have an effect on thiamin levels [47]. Thiamine in food, especially

processed meats, is also destroyed by sulfites or sulfur dioxide used as a preservative [49,51]. Experimentally-induced thiamine deficiency has also been studied in dogs and cats [44,50,52,53].

The metabolically active form of thiamine is thiamine pyrophosphate that plays an essential role in the intermediary metabolism of carbohydrate, and is especially involved in three enzyme systems [2]:

- a. Pyruvate dehydrogenase (converts pyruvate to acetyl coenzyme A);
- b. Alpha ketoglutarate dehydrogenase (catalyzes the conversion of alpha ketoglutarate to succinate in the Krebs cycle); and
- c. Transketolase (catalyzes the pentose monophosphate shunt).

Thiamine is thus essential for complete oxidation of glucose through the Krebs cycle (citric acid cycle or tricarboxylic acid cycle). As a consequence of thiamine deficiency, serum levels of pyruvate and lactate are increased, along with reduced red blood cell transketolase activity. Tissues dependent on glucose or lactate-pyruvate for energy, such as the brain and heart, are particularly compromised in thiamine deficiency. It still remains uncertain how thiamine deficiency leads to the phenomenon of selective vulnerability of neuronal cell death [2,52]. Impaired vascular perfusion might play a role in this disorder; results of experimental studies suggest that hemorrhages could be related to hemodynamic changes resulting from thiamine deficiency-induced vascular dysfunction [54]. In addition, events such as blood-brain barrier breakdown, N-methyl-D-aspartic acid receptor-mediated excitotoxicity, and increased reactive oxygen species have been implicated [55,56].

Clinical signs in dogs include anorexia, emesis, depression, wide-based hind limb stance, kyphosis, sensory ataxia, progressive spastic paraparesis, crouching hind limb gait, torticollis, head ventroflexion, circling, exophthalmos, generalized tonic-clonic seizures, profound muscular weakness, recumbency, opisthotonus, coma and death [48,53]. Patella reflexes are usually exaggerated, and there may be proprioceptive and menace deficits, tremors, and occasionally, nystagmus. Some dogs show signs of hysteria [53]. In cats, vestibular signs, head tremor, ataxia-dysmetria, transient seizures often precipitated by handling, depression, ventroflexion of the head with the chin almost touching the sternum (especially when the cat is suspended by the hind limbs), lying in a tight semicircular posture, dilated, poorly-responsive pupils, and absent menace response may be observed [50,57]. Cats with severe lesions may manifest semicoma, persistent crying, opisthotonus and limb spasticity, followed by death. Electrocardiographic abnormalities have been cited in dogs and cats, including bradycardia, tachycardia, sinus arrhythmias, QRS prolongation, P waves with notched peaks, elevation of the ST segment, and T-waves flattening or inversion [53]. Whole blood thiamine content is reduced in affected dogs [48].

Pathological findings in dogs and cats with experimental or spontaneous thiamine deficiency are similar and are characterized by polioencephalomalacia with bilaterally symmetrical spongiosis, necrosis, and hemorrhage of upper brainstem nuclei, primarily in periventricular gray matter [50,52,58]. The caudal colliculi are consistently involved and hemorrhagic or yellow-tan or brown malacic lesions may be seen macroscopically [48,50]. Gross lesions have also been noted occasionally in ventromedial and dorsomedial occipital cortex, dorsomedial parietal cortex, hippocampal gyrus, medial vestibular nuclei and cerebellar nodulus in dogs with experimentally-induced thiamine deficiency [52]. Microscopically, lesions involving the caudal colliculi consist of severe/total parenchymal necrosis with intense reactive changes associated with hypertrophy and hyperplasia of endothelial and adventitial cells, edema, gitter cell formation and intense microgliosis [48]. Spongy changes may be present in ventromedial and dorsomedial occipital cortex and dorsomedial parietal cortex, basal nuclei, red nucleus, oculomotor nucleus, vestibular nuclei, rostral olives, cerebellar peduncles, cerebellar nodulus and/or lingula, and cerebellar roof nuclei. Other findings include microvascular proliferation and occasional mild, lymphocytic perivascular cuffing. Spongiosis is due to hydropic vacuolation of the neuropil and myelin sheaths. This constellation of pathology varies with the stage of the disease: early, intermediate, and advanced lesions have been described in experimentally-induced thiamine deficiency in dogs [52]. Ultrastructurally, there is hydropic swelling of astrocytic processes and intramyelinic edema. In advanced stages, there is lysis of the neuropil, marked demyelination, accumulation of lipid macrophages, and variable axonal degeneration. White matter lesions are reportedly minimal and limited to the corona radiata adjacent to areas of cerebrocortical necrosis, and to medullary cores of folia within totally affected cerebellar cortex [52]. No spinal cord or peripheral nerve lesions have been observed in dogs or cats [48,50,52]. Myocardial degeneration has also been reported in hearts of affected dogs and cats [52,59]. In humans, thiamine deficiency may also lead to peripheral nerve axonal degeneration [60].

Prompt administration of thiamine hydrochloride, even in severely affected animals, can result in complete remission of clinical signs, e.g., 25 to 50 mg/day IM in dogs, and 10 to 20 mg/day IM, in cats, over several days; although learning deficits have been reported in cats that recovered from experimentally-induced thiamine deficiency [61].

### **Vitamin E Deficiency**

Vitamin E is a fat-soluble vitamin of plant origin. Alpha-tocopherol is the most active form of vitamin E and it appears to be

taken up preferentially by the CNS [62]. Alpha-tocopherol is incorporated into chylomicrons in the small intestine prior to absorption, and in the liver it is bound and recycled by alpha-tocopherol transfer protein and incorporated into low-density and very-low density lipoproteins. It is delivered to cells where alpha-tocopherol functions as an antioxidant and helps prevent free radical peroxidation and injury to cell membranes [2]. Deficiency can occur at any level of tocopherol metabolism. In humans, vitamin E deficiency is associated with axonal membrane injury leading to axonal degeneration of peripheral nerves, dorsal root ganglia and posterior (dorsal) columns. In dogs and cats, vitamin E deficiency appears to be rarely involved with pathology of the nervous system. At one time, degenerative myelopathy (especially in German Shepherds) was considered to be possibly related to vitamin E deficiency [23]; however Averill failed to find evidence for vitamin E deficiency in his group of dogs [63] and recent studies suggest that this association is unlikely (in fact serum alpha-tocopherol concentration was significantly higher in German Shepherd dogs with the condition) [64]. Additionally, vitamin E supplementation had no effect on clinical signs. Statistical studies in this report indicated that the concentration varied more widely in individual affected dogs than in unaffected dogs, irrespective of breed. Vitamin E deficiency has been reported in visually impaired Walker Hounds and Beagles that were fed a diet of table scraps [65]. Sensory retinal degeneration was found in all dogs, and severity of changes varied with age of the dog. Plasma, serum, and tissue concentrations of vitamin E were low in affected dogs. Lipofuscin accumulation was found in retinal pigment epithelium and neurons of the CNS. Findings were consistent with nutritional vitamin E deficiency and oxidative injury to photoreceptors of the retina. Changes in these dogs were similar to those described for central progressive retinal atrophy and equine lower motor neuron disease. Vitamin E deficiency has occasionally been associated with reports of myopathies in dogs and cats (see vitamin E-selenium-responsive myopathy). Serum vitamin E concentrations are reportedly lower in adult and immature Brittany Spaniels with hereditary canine spinal muscular atrophy [66]. Vitamin E deficiency has been implicated in distemper vaccination failures [67] and generalized lipofuscinosis in dogs [68].

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## **Neurovascular Disorders** (6-Feb-2003)

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### **Neurovascular Disorders**

Neurovascular disorders encompass those conditions that result in cerebrospinal ischemia, infarction, and hemorrhage. Various vascular and parenchymatous changes have been reported in dogs and cats in association with vascular anomalies (e.g., aneurysms, telangiectatic hamartomas), cerebral arteriosclerosis, mineral and pigment deposition, malacias and necrosis, cerebral infarction-thrombosis-embolism, inflammatory processes, cerebral hemorrhage, and vascular neoplasms, including intravascular lymphoma (malignant angioendotheliomatosis) [1,110]. Cerebral ischemia connotes insufficient blood supply to the brain to maintain normal cellular functions. It has been stated that ischemia can be viewed as hypoxia plus hypoglycemia [2].

Brain ischemia may be:

- a. focal resulting from narrowing/occlusion of cervicocranial vessels or from hypoperfusion of the brain associated with atherothrombosis or embolism, or
- b. global resulting from systemic hypoperfusion [3].

In atherothrombosis, a localized thrombus forms on an atherosclerotic plaque resulting in disruption of blood flow and subsequent ischemia and/or infarction. In embolism, a brain or spinal cord artery is suddenly occluded by embolic material, usually a thrombus that arises from a distant site such as the heart. Hypovolemia or cardiac pump failure causes a global decrease in cerebral blood flow and can lead to infarction in the border zones between major cerebral arteries (called watershed infarction). Impaired blood supply to the brain results in a decline in tissue  $PO_2$  levels, called stagnant hypoxia, which is tantamount to ischemia [4]. Cells in the central nervous system (CNS) show selective vulnerability to the effects of ischemia and hypoxia (often considered together as hypoxia-ischemia [2]). Due to the high demand of neurons for oxygen, neurons are first affected by hypoxia-ischemia followed by oligodendrocytes, then astrocytes, and finally vascular cells [4]. If neurons are the only cells affected, the tissue damage is termed "selective neuronal necrosis". If all cellular elements are affected, the lesion is called "pan-necrosis" or "infarction". The spinal cord is less sensitive to hypoxia-ischemia than is the brain [5], while neonatal animals are more resistant to hypoxia-ischemia than are adults [2]. Axons are more sensitive to hypoxia-ischemia than their myelin sheaths [2]. In general, the incidence of neurovascular disorders based on pathological studies is low in dogs and cats [1,6]. Yet several reports argue that neurovascular disorders may be more common than the literature suggests and that the increased availability of advanced imaging techniques has heightened the awareness of these often devastating conditions [7-9].

The following neurovascular disorders of the CNS will be discussed:

**Cardiac Arrest**  
**Feline Ischemic Encephalopathy**  
**Fibrocartilaginous Embolization**  
**Hemorrhage**  
**Hemorrhagic Myelomalacia**  
**Infarction**  
**Seizures and Cerebral Necrosis**  
**Traumatic Feline Ischemic Myelopathy**

## **Cardiac Arrest**

Cardiac arrest during anesthesia may have devastating effects on the brain. In one report involving 2 cats and 2 dogs, cardiac arrest of variable duration (for at least 7 to 8 minutes in one cat) occurred during anesthesia [10]. Post-operatively, animals showed blindness, sometimes accompanied by dilated pupils that later became miotic or anisocoric, and were variably unresponsive to light. Initially some animals were recumbent and opisthotonic with rigid limb extension. The hind limbs tended to relax within several days. Transient positional nystagmus was observed in one dog. Several animals were hyperexcitable and some had seizures. One 6 year old Domestic shorthair cat presented with a 2- week history of blindness following general anesthesia had normal pupillary light response and dazzle response [102]. Microscopically, extensive lesions of ischemic necrosis (characterized by neuronal cytoplasmic eosinophilia, shrinkage, nuclear pyknosis, and neuronal dissolution) were observed in the cerebral cortex, cerebellar vermis (involving Purkinje cells with astrocytic proliferation in the molecular layer), basal ganglia, thalamus, and caudal colliculi [10]. Hemorrhage into the cerebral cortex was observed, and ischemic necrosis was present in several cranial nerve nuclei (usually bilaterally symmetrical), the mammillary body, the interpeduncular ganglion, and the acoustic tubercle. Secondary Wallerian degeneration and/or edema of white matter were seen. Microcavitation of affected cerebral cortex occurred soon after the cardiac arrest. The distribution of lesions suggested a particular susceptibility of affected areas to hypoxia/anoxia. The most severe lesions occurred in the more dorsal convolutions of the cerebral cortex, especially those bordering the longitudinal fissure. The involvement of the basal ganglia and hippocampus also suggested specific tissue vulnerability. Cerebral malacia, also located in the cerebral cortex and in the region of the basal ganglia (caudate nucleus, internal capsule, and putamen), has been found in dogs and cats with chronic congestive heart failure associated with atrioventricular valvular insufficiency and intramural coronary arteriosclerosis [1,6].

In dogs and cats with cardiac arrest, the cerebrocortical necrosis may extend from the frontal to the occipital lobes, while the cingulate gyrus, ventral and lateral gyri (pyriform lobe and parahippocampal gyrus) are usually spared [2] and watershed areas (the border zones between major cerebral arteries) are particularly susceptible to hypoxic conditions [2,10]. Endogenous neurotransmitters and nitric oxide have been implicated in mediating neuronal necrosis [2,11,12]. However, the relationship of blood oxygenation and vascular occlusion to brain necrosis is incompletely defined [13]. Cortical laminar necrosis occurs in humans following cardiac arrest and may be detected and differentiated from hemorrhage using MRI [14]. In humans, the consequences of transient global ischemia can be predicted from a number of factors, including duration, completeness of the ischemic insult (e.g., some degree of residual perfusion gives a better outcome than total cardiac standstill), brain temperature (e.g., hypothermia has a neuroprotective effect against ischemia), and blood glucose levels (e.g., hypoglycemia improves recovery of energy metabolism and reduces accumulation of lactate with the result that ketosis improves tolerance to hypoxia and reduces delayed neuronal death) [4].

The type and distribution of lesions seen in these clinical cases of cardiac arrest were reportedly similar to those seen in dogs with experimentally-induced hypoxia (dogs were subjected to 15 minutes of cardiac arrest followed by resuscitation) [15,16]. The areas of the brain affected are also similar to those seen in other conditions involving energy deprivation of neurons, including hypoglycemia and cerebral necrosis associated with seizures [2].

Treatment protocols are not well defined in animals with brain injury following cardiac arrest but those used for cranial trauma (see Traumatic Disorders) might be considered. Prognosis is guarded to poor, although the blindness after cardiac arrest may be temporary. Seizures, anisocoria, facial and trigeminal paralysis were considered to imply a grave outlook [10]. A post-anesthetic cerebellar disease has been reported in Persian or Persian-cross cats 3 to 10 years of age with signs of mild to severe ataxia in all limbs with intention tremor, lack of menace response and delayed hopping reactions [106]. No other neurologic deficits were noted. The signs were non-reversible. Ketamine was the only anesthetic drug common to all cases. A possible genetic component altering the properties of cerebellar NMDA (N-methyl-D-aspartate) receptors and subsequent cytotoxicity following binding to ketamine or one of its metabolites was proposed. Histopathology has not been studied to date.

## **Feline Ischemic Encephalopathy**

Feline ischemic encephalopathy (FIE) is an ischemic necrosis of cerebral tissue that occurs sporadically in male and female cats of all ages (e.g., from 7 months to 11 years), especially in summer months [17-21]. Clinical signs are usually acute in onset, non-progressive, and variable (probably reflecting location of lesions and associated brain edema), and typically suggest unilateral cerebral or brainstem involvement. Signs may include depression, head tilt, anisocoria, circling, seizures, and change in attitude/behavior, often to the point of aggression. Seizures are often the initial presenting or historical clinical sign [19,21], and they may be mild and/or of the partial category, and of low frequency [22]. Mydriasis and visual impairment may be present. Clinical signs may be modified or disappear with time (several days to weeks). Multiple episodes may occur.

Hematology, blood chemistries, and skull radiographs are usually normal. Cerebrospinal fluid (CSF) analysis may be normal or reveal a mild to moderate pleocytosis (usually monocytic) and mild protein increase. An increased proportion of large foamy macrophages has been observed in CSF from 2 to 7 months after onset of seizures [22]. A presumptive diagnosis may be made using MRI. In one study of 6 affected cats, T2 weighted MRI revealed mild-to-marked asymmetry of the cerebral hemispheres and bilateral, but asymmetric enlargement of the subarachnoid space, suggesting compensatory pooling of CSF over atrophied gyri and widened sulci, especially involving the temporal lobes [22].

Lesions are usually unilateral and may involve up to 75% of one cerebral and/or cerebellar hemisphere. Grossly, the involved hemisphere may appear atrophic and ridged with wide sulci [19,21]. The sunken, depressed area is often found in the parietal-temporal field of the cerebrum [2]. In some instances, there is loss of the pyriform lobe, amygdala, parahippocampal gyrus, claustrum, globus pallidus, putamen, internal and external capsules, and subcortical white matter, with associated moderate dilatation of lateral and third ventricles [21]. These gross changes are frequently found in cats with an extended clinical course. Histopathological findings are characterized by severe parenchymal atrophy and cystic degeneration, gliosis, and phagocytic macrophage infiltration. Perivascular, lymphocytic cuffing around small capillaries has been seen [21]. The major area of infarction is frequently in the distribution of the middle cerebral artery. Vascular occlusive lesions, including thrombosis and vasculitis, have been found only occasionally [2]. Affected animals do not have cardiomyopathy.

The cause of this enigmatic ischemic condition has been uncertain. Clinical similarities between FIE and *Cuterebra* infection of the brain were noted some time ago [17], and preliminary evidence for this pathogenesis has now been reported [2]. More recently, 10 cats with primary CNS infection by larvae of *Cuterebra* flies were documented at Cornell University [112]. Clinical abnormalities noted in all cats were progressive and most commonly consisted of depression, blindness, and behavior changes. Affected cats presented in July through September. The diverse histopathological changes were unique to this aberrant migration and consisted of a combination of five characteristic features: parasitic track lesion in 7 cats, superficial laminar cerebrocortical necrosis (associated with dark and shrunken neurons) in all cats, cerebral infarction in 8 cats, subependymal rarefaction and astrogliosis with or without ependymal cell loss in 7 cats (especially involving the lateral ventricles), and patchy subpial astrogliosis restricted to the brain stem and spinal cord in 7 cats. The last four-mentioned changes occurred throughout the parenchyma unassociated with the track lesion or the parasite in the affected tissue. The larvae were recovered most commonly in the region of the olfactory bulbs and peduncles, optic nerves, and cribriform plate, suggesting entry from the nasal cavity. Many of the changes noted were suggestive of a toxic factor elaborated by the parasite and/or the host tissues and circulated within the CSF, as well as vascular compromise as a component in those cats with brain infarction. Based on the prevalence of infarction associated with this syndrome, the lack of reported cases of such lesions in regions of the world devoid of the fly (e.g., Australia and New Zealand), and the clinical and pathological similarities to FIE, it seems likely that aberrant *Cuterebral* larval migration in the brain is the putative cause of feline ischemic encephalopathy.

Treatment is largely supportive. Prognosis is often favorable since many of the signs seen initially will ameliorate; however, behavioral changes and uncontrollable seizures may persist.

### **Fibrocartilaginous Embolization**

Fibrocartilaginous embolization (FCE) is an ischemic necrosis of spinal cord parenchyma that has been associated with fibrocartilaginous emboli in spinal cord vasculature of dogs [23-29]. The disorder has been reported mainly in dogs of either sex, immature as early as 4 months of age [30] and adult, of small and large non-chondrodystrophoid breeds. Almost 50% of confirmed cases have been giant-breed dogs [31]. Young Irish Wolfhounds (between 8 and 13 weeks of age), of either gender (but especially males) appear to be predisposed to this condition [32]. In small breeds, the Miniature Schnauzer is often affected [33]. FCE has been reported less commonly in cats [34-37,107].

The pathogenesis is not clear. Intervertebral disk material is considered to be the source of the fibrocartilage and it has been hypothesized that disk material may somehow be "injected" into spinal cord vessels. For a review of several hypotheses, see Cauzinille [31]. The fact that this disorder occurs in young adult non-chondrodystrophoid breeds of dogs that are not prone to disk disease at this age is enigmatic (approximately 80% of affected dogs are between 3 and 6 years of age) [31], especially since the condition has not been reported in chondrodystrophoid breeds of dogs, which are at high risk of disk disease. Fibrocartilaginous emboli have been demonstrated, however, in pulmonary vessels of chondrodystrophoid breeds of dogs with signs of clinical disk disease. The role of trauma remains unclear. According to one review, approximately 60% of confirmed canine cases had an antecedent history of trauma or exercise [38].

Onset of signs is typically hyperacute, usually within minutes to several hours. Signs usually do not progress beyond the first 24 hours [33], except for those rare cases in which hemorrhagic myelomalacia develops. Clinical signs of FCE will reflect location of the lesion within the spinal cord. Signs may be unilateral or bilateral, depending on the site of infarction and the degree of damage [29]. While any level of the spinal cord may be affected, cervical or lumbar cord segments are commonly involved, especially at the level of the cervicothoracic (see cervicothoracic syndrome) and lumbosacral (see lumbosacral syndrome) intumescences [31]. Infarction at the level of the cervicothoracic or lumbosacral spinal cord may result in a neuropathic syndrome as a result of necrosis of ventral horn cells within the spinal cord gray matter. Clinical signs will be characterized by depressed reflexes, reduced muscle tone, and muscle atrophy after 5 to 7 days. According to the level of the spinal cord injury and its extent, Horner's syndrome and or loss of the cutaneous trunci reflex may be noted. If the lumbosacral cord is involved, there may be paralysis and analgesia of the tail, anal sphincter, bladder and rectum. Affected animals do not typically show evidence of pain, although there may be historical reports of pain or discomfort prior to neurological deficits [9]. Signs of a thoracolumbar syndrome will be seen with spinal cord lesions between T3 and L3 cord segments. In cats, emboli have been reported in cervical and lumbosacral cord regions.

Plain radiographs are normal. Myelography is usually normal but if performed early it may suggest slight cord swelling (e.g., from edema or hemorrhage), at or rostral to the level of the lesion. CSF analysis may reveal an elevated neutrophil count within a few hours of clinical onset, and protein levels in CSF may be slightly increased. Other neuroimaging techniques, for example, MRI, may become useful, sensitive tools for diagnosing FCE in the future [31].

Pathologically, malacia and necrosis of spinal cord gray and white matter are present, often extending over several spinal cord segments. The margins of the lesions tend to be well delineated from normal tissue, with new vascular proliferation and macrophage infiltration evident within a few days [39]. Gitter cells are prominent in the infarcted areas and cavities may form [37]. There may be evidence of emboli in one or more spinal cord vessels (arteries, arterioles and/or veins) or occasionally, in nerve root vasculature, having histological and histochemical staining characteristics of fibrocartilage seen in intervertebral disks [39]. Infarcted areas are usually ischemic but may be hemorrhagic. In addition to the phagocytic mononuclear cells, neutrophils are often abundant within the lesions. Lesions are frequently asymmetric [29]. Gritty cholesterol masses, presumably secondary to myelin breakdown products within infarcted areas, were found in spinal cord white matter in 3 dogs with fibrocartilaginous emboli [23].

Prognosis is guarded and depends on the location and extent of infarction, as well as prompt initiation of medical therapy [40,41]. Animals with extensive gray matter involvement of the cervicothoracic and/or lumbosacral spinal cord segments and those that subsequently develop hemorrhagic myelomalacia have a poor prognosis. Conversely, animals with upper motor neuron signs (associated with a lesion between T3 and L3) have a better prognosis [40,42]. Prognosis may also be related to dog size. In one study, mortality in Miniature Schnauzers associated with fibrocartilaginous embolic myelopathy was significantly lower than mortality rates reported for affected large and giant breeds [33]. Treatment using a high-dose of methylprednisolone succinate (MPS) has been recommended - slow intravenous bolus of MPS, 30 mg/kg, followed by 5.4 mg/kg/hour for 24 to 48 hours [31]. Patients should receive the MPS as soon as possible after onset of neurological signs (e.g., within 6 hours) to maximize chances of recovery. Any improvement should be apparent in 10 to 14 days [43]. Residual effects are common [33,40,41]. Excellent nursing care is essential for non-ambulatory patients (see Spinal Trauma for more information).

## **Hemorrhage**

In cerebral hemorrhage, blood leaks from the vessel (usually a small artery) directly into the brain, one of the ventricles, or the subarachnoid space. Epidural, subdural, subarachnoid and intraparenchymal hemorrhages may be observed in dogs and cats following head injury [44,45] and bleeding into the inner ear is not infrequent [46]. Note that the term "extradural" is more anatomically correct than "epidural" because of absence of any epidural space within the cranium [108]. Variably sized perivascular hemorrhages will also be seen in an area of contusion. Contrecoup hemorrhages result from tearing of leptomeningeal and parenchymal blood vessels [44]. Subdural hematomas may occur as focal intradural mass lesions or as diffuse lesions over the cerebral cortex, sometimes associated with massive accumulations of blood [45,47]. Subdural hematomas may be a complication of hydrocephalus. It has been suggested that hydrocephalus resulting in a widened subarachnoid space may predispose to tearing of cerebral vessels where they cross the subdural space [108]. In some centers, hemorrhage associated with hydrocephalus is observed as a necropsy finding more frequently in the ventricles due to tearing of the internal capsule [108]. Subarachnoid hemorrhage is a common consequence of cranial trauma in animals and is usually associated with extensive parenchymal damage [44]. Hemorrhage into the brain substance (intraparenchymal) from damaged vessels is commonly observed. This form of bleeding may be short-lived due to vessel spasm and

microthrombi formation [48]. Brain hemorrhages may quickly become space-occupying masses (hematomas) that, like brain tumors, compress brain parenchyma, and if unchecked, may lead to widespread brain edema, brain herniation, mid-line shifts, ischemia, brainstem compression and development of deep pontine hemorrhages (Duret hemorrhages) [44]. As herniation progresses, petechial or small ecchymotic hemorrhages may be found in the medulla oblongata and in the herniated cerebellar verian lobe.

In spinal trauma, subdural hemorrhage is commonly found. Epidural hemorrhage is a frequent finding in severe disk disease. Petechial hemorrhages are commonly observed in injured spinal cord segments (see Disk Disease and Spinal Trauma). Dural laceration, epidural, subdural, and intramedullary hemorrhage, along with malacia and swelling of the spinal cord at the T12 - 13 interspace, were reported in a racing Greyhound that fell in a race and developed acute hind limb paralysis [49]. Subperiosteal vertebral hematoma in the dog, unassociated with spinal trauma, appears to be a rare vascular accident of an epidural nature [50]. In this report, a 13 month old dog had non-weight bearing paraparesis and total anesthesia to the hind limbs, anus and tail. Myelography revealed an extradural compressive lesion in the body of L3. At necropsy, a subperiosteal hematoma encircled the cord on all but the ventral aspects. There was no evidence of free blood in the spinal canal. At the level of L3, the spinal cord appeared swollen, with axonal degeneration, hematomyelia, and gliosis. The cause of the hematoma was not determined. Interestingly, the authors reported a second case in a 7 year old Labrador Retriever with identical signs and necropsy findings [50].

In contrast to the high incidence in man, massive intracerebral hemorrhage resulting from spontaneous rupture of vessels and/or saccular aneurysms is rarely reported in animals [1,51,52]. In humans, this type of hemorrhage is usually associated with hypertension and degenerative and fibrotic changes in the intracerebral arteries. Neurological signs attributable to strokes (presumably hemorrhagic) have been seen in cats with severe systemic hypertension (signs included acute blindness and retinal hemorrhage/detachment) [53]. In dogs, spontaneous intracranial hemorrhages tend to be single, located in the cerebrum, and often in the area of the hippocampus-amygdala [44,51]. Cerebrovascular microaneurysms and variably sized ring-like hemorrhages are sometimes seen in older dogs, usually from 9 to 11 years of age, or older, in association with an amyloid (conophilic) angiopathy [52,54,55]. In these dogs, amyloid deposits were observed mostly in the wall of cerebral arterioles and capillaries showed hyaline degeneration. The accumulation of amyloid fibrils measuring about 10 nm in diameter was seen in the cerebral vessel wall by electron microscopy. The hemorrhages, which were quite large in some dogs, were associated with the vessels involved in the amyloid angiopathy [54]. The hemorrhages occurred mainly in the upper layers of the cerebral cortex. Cerebellar cortex, white matter, subcortical and brainstem gray matter were rarely involved. Clinical signs included seizures, behavioral changes, and motor disturbances. In a dog with a 2 year history of exophthalmos occurring 2 years after head trauma, an enlarged cavernous sinus and associated ophthalmic plexus were believed to represent an arterialized aneurysm, most likely the result of traumatic arteriovenous fistulization [56]. Intracranial and intraspinal hemorrhage has been occasionally reported in dogs in association with arteriovenous vascular malformations e.g., telangiectatic hamartomas and angiomas [1,57,58]. Hemorrhage into primary and secondary brain tumors is frequently observed in dogs, especially oligodendrogliomas, glioblastomas, ependymomas, and hemangioendotheliomas [1]. Hemorrhage within a pituitary adenoma leading to secondary compression of the hypothalamus resulted in signs of hyperthermia, hypernatremia and collapse ("pituitary apoplexy") in a 7 year old female German Shorthaired Pointer [103]. Hemorrhage has been observed in the CNS of dogs with intravascular lymphoma (malignant angioendotheliomatosis) [110,116]. Intracystic hematomas have been found in dogs with intracranial intra-arachnoid cysts [111].

Miscellaneous hemorrhages of diverse etiologies have been reported in the CNS of dogs and cats, including migrating parasitic disorders, e.g., cuterebriasis in dogs and cats [1,59]; protozoan infections, e.g., toxoplasmosis in dogs [1], bacterial meningitis [1]; viral diseases, often associated with attendant vasculitis, e.g., canine hepatitis [1], parvovirus [60], and canine herpes virus [61]; nutritional disorders, e.g., thiamine deficiency in cats leading to necrosis and hemorrhage of the hippocampus, midbrain, and medulla oblongata [1]; toxins, e.g., warfarin poisoning [62]; systemic metabolic disorders, e.g., disseminated intravascular coagulopathies, platelet dysfunction, and coagulation factor deficiencies [7,63]; infarction with diapedetic hemorrhages associated with thromboemboli, septic thrombi or neoplastic emboli [1,64]; and chronic serum hyperosmolality, e.g., diabetes mellitus or hypernatremia, in which shrinkage of brain tissue may cause tearing of vessels, leading to subarachnoid or subdural hemorrhage [65]. Cerebral hemorrhage has also been found in dogs with salt poisoning [66].

CNS hemorrhage may occur after therapeutic or diagnostic procedures. Mild, moderate or severe patchy hemorrhagic leptomeningitis was seen at 24 hours after subarachnoid injections of non-ionic contrast agents iopamidol or metrizamide [67]. Variable degrees of hemorrhage have been reported in intracranial pressure monitoring [63]. Hemorrhagic complications resulting in progressive seizural activity and respiratory arrest were reported with L-asparaginase

administration for the treatment of tumors [68]. In this instance, a triangular wedge of hemorrhagic infarction was found in the cerebrum of a 9 year old Labrador Retriever - the base of the triangle was oriented along the surface of the cortex while the apex extended into the white matter. Additional findings in this dog included multifocal hemorrhagic foci, fibrinoid degeneration of vessels, and thrombosis. A drug-related deficiency in serum antithrombin III may have predisposed this dog to hemorrhagic thromboembolism.

Onset of signs in animals with sudden hemorrhage is usually acute [7,69]. Clinical signs seen will reflect the location of the hemorrhage and development of any secondary effects, e.g., brain swelling and herniation. Involvement of the pyriform lobe or ventral region of the temporal lobe may cause brainstem compression leading to ipsilateral vestibular signs [69]. However, in one review of 17 dogs with cerebrovascular disease, all dogs in which hemorrhage was a dominant pathologic finding had evidence of a focal neurological deficit [7]. Presence of macrophages containing red blood cells or hemosiderin ("siderophages") in CSF may suggest a recent hemorrhagic episode, although these cells may persist for weeks or months [44]. Coagulation profiles, including platelet count, prothrombin time, activated partial thromboplastin time, thrombin time, and fibrin split products, and specific coagulations factors (e.g., plasma von Willebrand factor antigen) should be performed in animals with suspected coagulation disorders [7,63]. Prognosis of animals with hemorrhage is guarded. The advent of advanced imaging techniques, such as magnetic resonance imaging and computerized tomography, should facilitate the diagnosis of cerebral hemorrhage, cerebral ischemic infarction, and aneurysms in animals [8,56,70,71]. Reports on treating hemorrhage in animals are limited, although successful surgical removal (craniectomy and surgical drainage) of a subacute subdural hematoma has been reported [71].

### **Hemorrhagic Myelomalacia**

This destructive spinal cord lesion is probably the most undesirable complication of spinal trauma. Synonyms include progressive diffuse myelomalacia, progressive hemorrhagic myelomalacia, hematomyelia, ascending syndrome, and ascending cord necrosis. This condition may occur within a few hours to one day after the initiating injury, such as external spinal trauma, or more commonly, acute, massive intervertebral disk extrusion. In one study, type III disk protrusion, in which disk material spreads along the epidural space for a distance of one or more vertebrae and may completely encircle the dura, was found in 7 of 8 affected dogs [72]. Hemorrhagic myelomalacia may also occur after fibrocartilaginous embolization [109]. The thoracolumbar spinal cord is usually involved. Clinical signs reflect the nature and level of the lesion. Initially, with a thoracolumbar cord lesion, an animal will show signs of acute onset, total paraplegia with exaggerated pelvic limb reflexes [73]. As a result of edema and hemorrhage, the cord malacia can descend to involve the lumbosacral segments, and clinical signs of flaccid paraplegia with pelvic limb atonia and areflexia will develop within 2 to 3 days. The tail will be flaccid and the anus dilated and unresponsive to stimuli. Pain perception is absent in all these areas. As the disorder progresses rostrally, the thoracic limbs may become flaccid and analgesic, bilateral Horner's syndrome may occur, and a line of analgesia may be detected at the cranial thoracic region [74]. Breathing may become diaphragmatic. If the spinal cord malacia ascends to lower- or mid-cervical levels, respiratory paralysis will occur, followed by death. The myelographic signs include a variable degree of contrast medium infiltration into the spinal cord and/or spinal cord swelling [109].

The pathological lesion is a combination of ischemic and hemorrhagic infarction of spinal cord parenchyma. In areas of total transverse necrosis (involving both neural and mesenchymal elements), the disruption of normal architecture may be so marked that anatomical divisions of gray and white matter are lost. There is diffuse softening, hemorrhagic infiltration, extreme demyelination, and marked polymorphonuclear infiltration in the cord substance. Neurons show ischemic cell changes ranging from loss of Nissl substance and a prominent nucleolus to shrunken cells with homogeneous pink neuronal cytoplasm and pyknotic nuclei, often with small basophilic dots representing degenerating axonal terminal boutons. Some degenerating neurons are vacuolated. Eventually, only a faint cell outline (ghost cell) is seen. The majority of intramedullary blood vessels may be necrotic. Large accumulations of lipid phagocytes may be seen in some segments. In less severe lesions, localized infarcts of the white matter that are triangular in shape with the apex to the periphery may be present [72]. Hemorrhagic myelomalacia is characterized by rostral or caudal extension of hemorrhage and necrotic tissue in the central canal area or at the base of the dorsal funiculus. Extramedullary vessels (arteries and veins) may be thrombosed or ruptured, resulting in severe subdural and subarachnoid hemorrhage. Intraradicular hemorrhage is often seen and nerve roots may show evidence of Wallerian degeneration. The underlying mechanism for the proposed occlusive vascular damage is uncertain, although vasospasms and reduced collateral circulation have been implicated [72], perhaps secondary to release of catecholamines [74].

Spinal cord damage is permanent. There is no treatment. It should be noted that this condition could develop even after immediate surgical decompression of acute disk extrusion.



## Infarction

Infarction or necrosis (malacia) of the CNS parenchyma may result from cerebrospinal vascular occlusion associated with an embolus. The embolic material may represent white platelet-fibrin and red erythrocyte-fibrin thrombi, cholesterol crystals, fragments of atherosclerotic plaques, calcified fragments of valves and plaques, air, fat, myxomatous tumor fragments, or bacterial vegetations or other foreign bodies including parasites [3]. Miscellaneous occlusive conditions that can cause brain ischemia in humans include coagulation disorders, immunological abnormalities and vasculitides [3]. Similar conditions are rarely seen clinically in dogs and cats [53]. Some infarcts are devoid of blood and therefore pallid (pale infarction). Others show extravasation of blood from many small vessels within the infarcted tissue (red or hemorrhagic infarction) [75]. In one report of canine cerebrovascular disease, most infarcts were hemorrhagic [7]. Based on published reports and necropsy studies, the incidence of CNS infarction is relatively low in dogs and cats [1,6]. Infarction most commonly occurs in association with fibrocartilaginous emboli in dogs and with ischemic encephalopathy in cats. Hemorrhagic myelomalacia is sometimes associated with acute, severe spinal cord trauma, such as intervertebral disk extrusion. Aortic thromboemboli in cats typically results in neuromuscular pelvic limb ischemia, rather than spinal cord infarction (see ischemic neuromyopathy). Note that one potential complication of hyperadrenocorticism in dogs is thromboembolism, possibly related to coagulation protein loss in urine, and signs of pelvic limb weakness, pain and collapse as a result of occlusion of the distal aorta and/or the iliac arteries [104].

Cerebellar infarction caused by primary arterial thrombosis has been reported in a 12 year old German Shepherd dog with acute onset of seizures, moderate opisthotonus, and menace deficit in the left eye [76]. The dog remained recumbent for several days before slowly improving to the point it could stand unassisted. At this time, the dog showed predominantly cerebellar signs, including swaying backward and forward, lurching to either side, ataxia-dysmetria, and falling. Grossly, a soft, hemorrhagic area was found in the rostral and middle parts of the left cerebellar hemisphere. Microscopically, a well-demarcated area of hemorrhagic necrosis was present with marked disruption of the granular layer and accompanying neuronal and Purkinje cell degeneration. Moderate diffuse reactive astrocytosis was admixed with a primarily mononuclear cell infiltrate. In less severely affected areas, a moderate multifocal to coalescing spongiosis was seen primarily within gray matter. A mural thrombus was found in the rostral cerebellar artery. Interestingly, mild to moderate myocardial degeneration was also noted. A similar case was reported in an 11 year old, female Shetland Sheepdog, 4 days after an acute onset of seizures, mental depression, circling to the left, postural deficits of the right limbs, and a right menace deficit [77]. CSF was clear and colorless and protein content was 35 mg/dl with normal cell count. Using CT scans, a ring-enhancing, intra-axial lesion associated with edema and non-uniform ventricular compression was identified in the left frontal lobe. An area of ill-defined hyperdensity, compatible with hemorrhage, was seen on corresponding CT images before contrast enhancement. At necropsy, a focal, hemorrhagic infarct, characterized by liquefactive necrosis, marked gliosis and neovascularization, was found. The etiology of the infarction could not be identified. The CT findings were similar to those seen in man with cerebral infarction due to embolic occlusion and subsequent hemorrhage. MRI scans may be better than CT in the diagnosis of cerebral infarction in the acute phase (lesions <1 week duration) [77].

Venous thrombosis is rarely reported in the veterinary literature. As a result of the extensive cerebral venous network and presence of collateral vessels in animals and humans, thrombosis must be extensive before blood flow becomes greatly reduced and hypoxia-ischemia ensues [78]. A multitude of different conditions can cause venous thromboses in humans, including infections, altered hormonal status in young women during pregnancy, the puerperium, or associated with the intake of oral contraceptives, altered state of coagulability, congenital or congestive heart disease, and certain hematological disorders such as thrombocytopenia [78]. Cerebral hemorrhagic infarction associated with venous thrombosis was found in a 10 year old crossbred bitch with a history of peracute onset of seizures, left-sided hemiparesis and compulsive circling to the right [79]. The direct and consensual pupillary light reflex was absent in the left eye. Grossly, the right head of the caudate nucleus and rostral diencephalons were hemorrhagic and edematous. The right caudate nucleus was the most severely affected area and was characterized by hemorrhage, edema, and ischemic neurons. The right optic tract was severely edematous and associated oligodendroglial nuclei were pyknotic. Astrocytes were swollen and surrounded by vacuoles. Medium to small diameter blood vessels within the affected regions showed fibrinoid necrosis, erythrocytic diapedesis, and fresh fibrin thrombi. Perivascular accumulations of a few neutrophils and macrophages were seen at the margins of the hemorrhagic lesion as well as in the neuropil of the right caudate nucleus. There was an occluding thrombus in the right basal vein extending from the rostral perforating substance to the dorsolateral branch of the basal vein. At the rostral limits, the thrombus had undergone organization and endothelial-associated recanalization. The left basal vein contained a fresh multilaminated occluding thrombus at the level of the hypothalamus. The etiology of the thrombi was not determined, although special stains failed to reveal bacteria or fungi in any thrombi. In humans, occlusion of a cerebral vein may lead to an infarctive stroke. The slower evolution of signs and its greater epileptogenic and hemorrhagic tendency favors venous over arterial thrombosis [75].

In contrast with humans, infarction in dogs and cats is rarely seen associated with atherosclerosis (arterial xanthomatosis) but when it does occur, it may be as a complication of hypothyroidism (in dogs) [1]. Atherosclerosis usually involves the intima of muscular and musculoelastic arteries and microscopically, the lesions include smooth muscle cells, collagenous and elastic fibers, fat-storing foam cells, extracellular lipids, cholesterol, calcium and amorphous debris [1]. One report on primary hypothyroidism involved a 6 year old Doberman Pinscher presented with sudden onset of seizures, disorientation and circling [80]. The dog had an 18 month history of episodic head tilt and ataxia. The condition deteriorated so that the dog was recumbent and comatose with marked extensor rigidity. Serum T3 and T4 values were low and cholesterol values were very high (2,130 mg/dl). CSF analysis was normal. An EEG trace revealed diffuse flattening in all leads, except for periodic spike- and slow-wave discharge associated with the right frontal lobe of the cerebral cortex. Grossly, both lobes of the thyroid gland were pale, small and thin. All visible arteries on the ventral and lateral surfaces of the brain were opaque yellow, firm, and tortuous. A shallow depression was noted over the dorsolateral aspect of the left parietal lobe of the cerebrum and the lumen of the branch of the middle cerebral artery supplying this region appeared obliterated. Microscopically, arteries throughout the body, especially in branches of the cerebral and coronary arteries had severe atherosclerosis characterized by intimal and medial fibromuscular thickening, cholesterol deposition, and accumulation of foamy macrophages and lipid vacuoles. In the brain, wide bands of pseudolaminar necrosis were seen in the peripheral gray matter of the left parietal lobe. The necrotic areas were composed of shrunken, degenerating neurons, small vacuoles suggestive of myelin degeneration, and numerous gitter cells. Similar focal areas were found in left and right cerebral cortices, along with multifocal, acute necrotizing vasculitis. A cholesterol granuloma was found in the white matter of the right parietal lobe. A few neurons in the caudal and medial vestibular nuclei were shrunken and degenerating. A lymphocytic thyroiditis was also present. In another study involving 21 dogs with atherosclerosis, common findings in dogs tested were hypercholesterolemia, lipidemia, and hypothyroidism [81]. Three dogs showed neurological signs, including disorientation, coma, circling to one side and loss of vision. Severe atherosclerotic changes and obstruction were present in the bifurcations of the arterial circle of Willis and rostral cerebral arteries and there was focal infarction in the cerebral hemispheres.

Cerebral infarction associated with septic thromboemboli has been reported in dogs [1,9]. In one report on 10 dogs, most were older than 5 years of age and there was an acute onset of severe neurological signs (cerebral syndrome with lateralizing signs) in 8 of the dogs [9]. CSF analysis revealed marked pleocytosis (including neutrophils) and elevated protein levels in 8 of 9 dogs tested. Seven dogs died or were euthanized, while 3 were treated successfully with antibiotics. Pathological changes included focal infarction, sometimes with abscess formation, vascular changes, thrombosis, and hemorrhage. In four dogs, a primary infection focus was found outside of the CNS. *Staphylococcus aureus* and  $\beta$ -*Streptococcus* were isolated in two cases.

Infarction has occasionally been observed secondary to embolic metastatic tumors cells in dogs [7], including mammary adenocarcinoma and other malignant neoplasms [1]. Multiple CNS ischemic infarction may occur in animals with intravascular lymphoma (malignant angioendotheliomatosis) associated with vessel thrombosis [110,113].

Infarction secondary to migrating parasites and/or parasitic emboli (see Parasitic Encephalomyelitis) is also occasionally reported in dogs, most frequently associated with heartworms (*Dirofilaria immitis*) [82,83]. In these reports, clinical signs were usually sudden in onset and included generalized seizures, blindness, ataxia, dysphagia, circling, and coma. Worms were found obstructing several vessels, including the anterior and posterior communicating arteries and the middle cerebral artery. Thrombosis of the anterior cerebral artery and meningeal arteries was also seen in one dog [82]. Variably sized areas of infarction were found in frontal, temporal, parietal, or occipital lobes of the cerebrum, depending on location of the arterial occlusion. In some dogs, the infarction was massive and involved virtually one complete cerebral hemisphere. Focal malacic lesions were occasionally present in the thalamus and lateral geniculate body. The malacic areas mainly comprised extensive ischemic changes in neurons, numerous foamy macrophages (gitter cells), and variable numbers of neutrophils. An intense granulomatous inflammation was sometimes found involving the arteries. Note that spinal cord infarction may also occur as a result of parasites and/or parasitic emboli.

Spinal cord infarction in cats has been induced by experimental X-irradiation [84]. In this study, the thoracolumbar spinal cord of 4 cats was subjected to 4000 RADS of X-irradiation. Between 3 and 5 months later, the cats developed hind limb weakness, showed proprioceptive deficits, and became uncoordinated. Microscopically, small infarcts were found in the white matter of the irradiated area of spinal cord, accompanied by neuronal death and edema of the gray matter close to the central canal. Ultrastructurally the infarcts were shown to stem from necrosis and thrombosis of small blood vessels. While CSF studies may suggest septic, neoplastic or parasitic etiologies, antemortem diagnosis of ischemic or hemorrhagic infarcts are more likely to center on the use of specialized imaging techniques, such as MRI [77,85,113]. Prognosis appears to be very guarded.

To date, detailed treatment strategies are lacking in animals. In humans, ischemic stroke management may include [3]:

- a. recanalization (thrombolytic therapy) of occluded vessels,
- b. maximizing blood volume and cerebral blood flow and reducing blood viscosity,
- c. maintaining sufficient perfusion pressure (through careful control of blood pressure, reduction of cerebral edema, and lowering of intracranial pressure) and
- d. blocking the progression of occlusive processes using anticoagulants and agents that alter platelet function.

### **Seizures and Cerebral Necrosis**

In humans, severe seizure activity is frequently associated with cognitive problems and with widespread neuronal ischemic necrosis in the neocortex, hippocampus and other selective neuronal populations [11,86-88]. This selective distribution may reflect a disruption of neuronal energy metabolism. A similar neuronal vulnerability is seen in patients with hypoglycemia and cerebral ischemia [5,89], suggesting a similar pathogenesis for hypoxic-ischemic conditions. In humans, lesions induced by status epilepticus (SE) may be epileptogenic by leading to misdirected regeneration. Major increases in cerebral blood flow (CBF) protect the brain in early SE, but CBF falls in late SE as blood pressure falters [87]. At the same time, large increases in cerebral metabolic rate for glucose and oxygen continue throughout SE. Adenosine triphosphate (ATP) depletion and lactate accumulation are associated with hypermetabolic neuronal necrosis. Excitotoxic mechanisms mediated by both N-methyl-D-aspartate (NMDA) and non-NMDA glutamate receptors open ionic channels permeable to calcium and play a major role in neuronal injury from SE. Hypoxia, systemic lactic acidosis, CO<sub>2</sub> narcosis, hyperkalemia, hypoglycemia, shock, cardiac arrhythmias, pulmonary edema, acute renal tubular necrosis, high output failure, aspiration pneumonia, hyperpyrexia, blood leukocytosis and CSF pleocytosis are common and potentially serious complications of SE [87].

The association between seizures and brain pathology remains enigmatic in dogs and cats. In one report of neuropathological changes in the brains of 40 dogs with seizures, 12 cases of which were considered to be idiopathic epilepsy including several dogs with status epilepticus, Palmer [90] found no evidence of neuronal ischemic changes, and concluded that seizures, per se, did not appear to result in brain pathology. Summers and colleagues reported a similar experience [2]. More recently, a morphologic and morphometric study of dogs with medically intractable epilepsy failed to find evidence of temporal lobe pathology [105], although heterotopic neuron clusters were found in one affected dog, suggesting that neuronal migration disorders might be a contributing factor to the epilepsy. There are several reports of seizures and cerebral necrosis or polioencephalomalacia in dogs, with selective involvement of areas in the brain suggestive of hypoxia-ischemia, including neocortex, hippocampus, pyriform cortex, basal nuclei and thalamic nuclei [91-96,115]. Microscopic changes include neuronal degeneration characterized by numerous eosinophilic shrunken nerve cells with granular cytoplasm, perivascular edema, cavitation of the neuropil, capillary hyperplasia, variable mononuclear cuffing, and gliosis. Fibrillary astroglial scars were seen in dogs that had a prolonged clinical course (e.g., seizures over 2 to 3 weeks). In some cases, the large pyramidal cells of the hippocampus (especially the H2 and H3 fields) were affected. The cortical lesions often had a disseminated, laminar, or pseudolaminar pattern. In some instances, there were areas of massive gray matter malacia with complete necrosis of cells with macrophage infiltration or cavities lined with astroglial fibers. None of these reports could establish if the lesions were the cause or the result of the seizures, although in one 5 week old puppy with hippocampal necrosis associated with canine distemper infection, acute neuronal changes in areas of more chronic lesions suggested disrupted neuronal metabolism by a synergistic effect of canine distemper virus and hypoxia-ischemia associated with status epilepticus [95].

There has been a recent clinicopathological report of 38 cats with either generalized or complex-partial seizures, of acute onset and rapid progression [97]. There was no sex or breed predisposition. Most cats were between 1 and 6 years of age (mean age 35 months). The seizures were often recurrent and presented as clusters or status epilepticus later in the course of the disease. Fourteen cats died spontaneously, and 24 were euthanized. Laboratory testing, including CSF analysis, was normal. Histopathological examination revealed bilateral lesions restricted to the hippocampus and occasionally the pyriform lobe. The lesions seemed to reflect different stages of the disease and consisted of acute neuronal degeneration to complete malacia, affecting mainly the layer of the large pyramidal cells but sometimes also the small neurons of the dentate gyrus and pyriform lobe. In most cats, the neurons were shrunken and contained brightly eosinophilic cytoplasm and pyknotic or lytic nuclei. Central chromatolysis with eccentric, pyknotic nuclei was sometimes seen. Occasionally, there was marked infiltration of vessels with lymphocytes and histiocytes. Microgliosis and astroglia were prominent. The clinical, neuropathological, and epidemiological findings suggested that the seizures in these cats were triggered by primary structural brain damage, perhaps resulting from excitotoxicity, and were not the result of idiopathic seizures. The cause remained unknown, but epidemiological analysis suggested an environmental factor, probably a toxin.

Unequivocal brain lesions associated with seizures have been reported, however, in an epilepsy-prone colony of beagle dogs that died as a result of the disorder [98]. Grossly, various degrees of brain swelling with flattening of the cerebrocortical sulci, and sometimes coning of the cerebellum with compression of the caudal cerebellar folia, were seen in a few dogs. Approximately 50% of the 68 dogs had a relatively specific pattern of acute brain damage on microscopic examination. In all affected areas, there was a triad of lesions consisting of perineuronal and perivascular astrocytic swelling, perineuronal basophilic incrustations, and ischemic cell change in neurons, especially the small cells. The lesions were often bilateral but asymmetrical. In the cerebral cortex, the rostral cerebrum was usually more severely involved than other areas, particularly the medial aspect of the frontal lobes and the cingulate gyrus. With increasing severity the lesions extended to the depths of the sulci and to the tips of the gyri of the lateral and dorsolateral convexities of the cerebrum. The most common areas of involvement were the cerebral cortex (especially neurons in layers II and III), basal nuclei (especially the globus pallidus, bilaterally), claustrum, amygdala, septal nuclei, dorsal thalamic nuclei, isthmus of the pyriform lobe, and hippocampus (particularly the dorsal horn, and especially involving the H1 field and endofolium). The cerebellum was affected only rarely. In addition, intraneuronal inclusions identical to Lafora's bodies found in myoclonus epilepsy of man were detected in thalamic nuclei of 6 dogs, but were considered to be incidental findings and unrelated to the seizures. Similar cortical findings have been reported in a 5 year old Shetland Sheepdog with a 3 year history of seizure episodes that ended in status epilepticus [99]. Grossly, both cerebral hemispheres, the hippocampal ventral horn and the posterior portions of the cingulate gyrus were reduced in size, and the lateral ventricles were mildly dilated. Microscopically, lesions were characterized by neuronal loss, gemistocytic to fibrillary astrocytosis, and vascular proliferation. The distribution was bilateral and symmetrical and involved the limbic parts of the cingulate gyrus, amygdala, dorsal and ventral hippocampus and dorsomedial nucleus of the thalamus. The most severe lesions were in the cingulate gyri and medial aspects of the frontal lobes, and the cortex in these areas was significantly reduced in size. The H1 field and endofolium of the hippocampus showed moderate neuronal loss and gliosis, while the dentate gyrus and H2 field were minimally affected. The extensive and chronic lesions were considered to be the result of recurring seizures during the course of the disease. Acute lesions such as edematous neuropil found in the thalamus may have resulted from the violent seizures prior to euthanasia. The type and distribution of lesions seen in these dogs were reportedly similar to those seen in dogs with experimentally-induced hypoxia [15,16]. Bilateral neuronal atrophy of the hippocampus with extensive gliosis and ventricular enlargement has also been reported in a 3.5 year old Poodle with epilepsy, although the author speculated that the lesions were the cause rather than the result of the seizures [100].

The infrequent reports of morphologic changes in dogs with seizures may suggest a degree of species insusceptibility and may also reflect such vagaries as intensity and frequency of seizures, duration, and degree of therapeutic control prior to death [2]. Reversibility of lesions may be another explanation. Reversible post-ictal imaging abnormalities (resolution of lesions was noted from 10 to 16 weeks) in the piriform/temporal lobes, characterized by varying degrees of hyperintensity on T2-weighted images and hypointensity on T1-weighted images, have been described in 4 dogs [114]. A surgical biopsy of the temporal cortex and hippocampus from an animal with an olfactory meningioma revealed edema, neovascularization, reactive astrocytosis, and acute neuronal necrosis. These histological findings are similar to the above-mentioned lesions seen in dogs with seizures. The authors emphasize that repeat imaging after seizure control may help differentiate between seizure-induced changes and primary multifocal parenchymal abnormalities. Similar reversible lesions have been documented in human patients following seizures [117]. The advent of high-resolution MRI may facilitate demonstration of changes such as hippocampal atrophy and abnormal signal intensities that are correlated with mesial temporal sclerosis in many human patients (in which seizures arise from the hippocampus or amygdala) [101].

### **Traumatic Feline Ischemic Myelopathy**

Summers and colleagues have described a unique ischemic myelopathy in cats in which affected animals were found with paralysis of the hind limbs and analgesia of the tail, anus, perineum, pelvic limbs, and caudal abdominal wall [39]. Necropsy studies revealed presence of abdominal trauma including sublumbar retroperitoneal hemorrhage, kidney avulsion or peritoneal hemorrhage. The vertebral column, vertebral canal, and spinal cord were grossly normal. Transverse sections of the spinal cord indicated discolored gray and soft areas of the central spinal cord extending from L2 through the caudal segments. Microscopically, there was severe, bilateral ischemic degeneration of the ventral gray columns including the central canal and associated gray and white matter and basal areas of the dorsal gray columns. The cranial extent of the lesion was from L1 to L3. Lesions varied from acute ischemic necrosis and macrophage infiltration to more chronic astrogliosis. The lesions were in the distribution of the branches of the ventral spinal artery. It was hypothesized that the cats were run over by vehicle tires causing contusion of the abdominal soft tissues and vasospasm/thrombosis of the lumbar arteries for a sufficient period to induce spinal cord ischemia. It was noted that ischemic infarction occurred in the lumbar epaxial muscles, which are also supplied by the branches of the same lumbar arteries.

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## Neoplasia of the Nervous System (6-Feb-2003)

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Neoplasia of the nervous system is reported frequently in dogs and cats [1]. In dogs, tumors of the nervous system occur with a frequency and a variety similar to that in people, whereas in cats, tumors are relatively less common, with the majority being meningiomas and lymphomas. The incidence of central nervous system (CNS) neoplasia in dogs is perhaps 1% to 3% of all canine necropsies [2-4]. Primary nervous system tumors originate from neuroectodermal, ectodermal, and/or mesodermal cells normally present in, or associated with brain, spinal cord or peripheral nerves. Secondary tumors affecting the nervous system may originate from surrounding structures such as bone and muscle, or may result from hematogenous metastasis of a primary tumor in another organ. Tumor emboli can lodge and grow anywhere in the brain, meninges, choroid plexus, or spinal cord. Dissemination or metastasis of CNS tumors is rare, but may occur via the cerebrospinal fluid (CSF) pathways, especially if tumors are located close to the subarachnoid space or ventricular cavities (e.g., choroid plexus papilloma, ependymoma, pinealoblastoma, neuroblastoma, or medulloblastoma), or via a hematogenous route, such as the dural sinus, with subsequent development of remote metastasis, usually in the lung. Tumors may also spread to surrounding tissues, especially bone, by direct extension. The osseous tentorium may be used as a reference point for localizing different areas of the brain within the cranial vault: tumors occurring in the brainstem and cerebellum may be called "infratentorial" or "posterior fossa" tumors, whereas those occurring in the cerebral hemispheres are often referred to as "supratentorial" or "anterior fossa" tumors. Neoplasias have been arbitrarily grouped as follows:

### Classification of Nervous System Tumors

#### Brain Tumors

- Overview
- Hematogenous Metastatic Brain Tumors
- Meningiomas
- Meningeal Sarcomatosis
- Malignant Histiocytosis
- Astrocytomas
- Glioblastoma Multiforme
- Oligodendrogliomas
- Medulloblastomas
- Ependymomas
- Choroid Plexus Papillomas
- Gangliocytomas
- Pituitary Tumors
- Suprasellar Germ Cell Tumors
- Malformation Tumors
  - Epidermoid and Dermoid Cysts
  - Intracranial Intra-arachnoid Cysts
  - Hamartomas
- Primary Skeletal Tumors

### Clinical Signs of Brain Tumors

#### Spinal Cord Tumors

- Overview
- Extradural Tumors
- Intradural-extramedullary Tumors
  - Nephroblastoma
- Intramedullary Tumors

#### Peripheral Nerve Tumors

### Diagnosis of Tumors of the Nervous System

#### Prognosis and Treatment

#### Skeletal Muscle Tumors

#### Paraneoplastic Disorders

### Classification of Nervous System Tumors

Classification of nervous system tumors in animals has followed the criteria used for human tumors [5]. Classification is primarily based upon the characteristics of the constituent cell type, its pathological behavior, topographic pattern, and secondary changes seen within and surrounding the tumor. Classification may be facilitated by use of immunocytochemical studies [6] and imaging techniques [7]. In general, primary tumors have a slowly progressive growth pattern, whereas, secondary, highly malignant, metastatic tumors, and bone tumors, frequently have a more acute progression. Although many

animal neoplasms have characteristics analogous with corresponding tumors in people, 15 - 20% of neuroectodermal tumors (especially gliomas) remain unclassified [5], many of which have a topographical relationship to the ventricular system and/or to the subependymal cell nests [1].

Immunocytochemical staining of neuroectodermal brain tumors reveals that up to 26% of the tumors are undifferentiated [6]. In general, tumors of the nervous system are more common in mature and older animals, although there are sporadic reports of brain tumors in animals less than a year of age [8]. Brachycephalic breeds are at risk for certain neuroectodermal tumors (see below). No gender predisposition for the various types of nervous system tumors has been clearly defined at this time.

### **Brain tumors**

**Overview** - Primary tumors of the nervous system in dogs and cats occur more often in the brain than in the spinal cord or peripheral nerves [1]. Commonly reported primary brain tumors in dogs are meningiomas, gliomas (astrocytomas, oligodendrogliomas), undifferentiated sarcomas, pituitary tumors, and ventricular tumors (choroid plexus papillomas and ependymomas [1,2,9-11]. Primary reticulosis (see granulomatous meningoencephalomyelitis), also described as gliomatosis [12] and microgliomatosis [1], although, perhaps incorrectly [4], is reported sporadically. Other primary brain tumors, such as malformation tumors (see below), tumors of nerve cells (e.g., gangliocytomas, neuroblastomas), pinealomas, craniopharyngiomas (a suprasellar ectodermal tumor that may destroy the pituitary gland), spongioblastoma (or "embryonal glioma", often with a periventricular orientation), and medulloblastomas (usually in the cerebellum), are rare [4]. Dogs over 2 years of age in the brachycephalic breeds with common ancestry, e.g., Boxers, English Bulldogs, and Boston Terriers, have the highest incidence of brain tumors among domestic animals, and of these, the glial tumors (including unclassified gliomas) are the most numerous [1,2,10,11]. Extension of primary nasal cavity tumors into the cranial vault is relatively common. Nasal tumor types include epidermoid carcinoma, adenocarcinoma, anaplastic nasal carcinomas or sarcomas, neurofibrosarcoma, neuroendocrine carcinoma, anaplastic chondrosarcoma, squamous cell carcinoma, and esthesioneuroblastoma. In contrast, tumors originating in middle or inner ear structures that extend into the brain are rare (see otitis media-interna).

### **Hematogenous Metastatic Brain Tumors -**

Hematogenous metastatic brain tumors originating from extracranial sites are common [1]. Hematogenous metastases in dogs frequently originate from carcinomas of the mammary glands, thyroids, bronchopulmonary epithelium, kidneys, chemoreceptor cells, nasal mucosa, squamous epithelium of the skin, prostate, pancreas, adrenal cortex and salivary glands. Less common intracranial metastases include transmissible venereal tumor in a 5 year old dog [13] and ovarian dysgerminoma in a 2 year old dog [188]. Recently, brain metastasis from a transmissible venereal tumor was reported in a 5 year old male crossbreed dog [13]. Common sarcoma metastases in dogs include hemangiosarcomas, lymphosarcomas, fibrosarcomas, and melanoblastomas. Brain metastases may accompany intramedullary spinal cord metastasis in dogs with hemangiosarcomas and lymphosarcomas [14]. In cats, metastases most frequently originate from mammary carcinomas and lymphosarcomas. Most instances of CNS lymphomas, especially in dogs, are manifestations of multicentric disease with frequent and extensive infiltration of the choroid plexus and leptomeninges [4,15], although a renal T-cell lymphoma with exclusive cerebral metastasis has been reported in a 5 year old Staffordshire bull terrier [182]. Neoplastic angioendotheliomatosis, or intravascular lymphoma (IVL), is a rare angiotropic large-cell lymphoma in which neoplastic lymphocytes proliferate within the lumina of blood vessels in the absence of a primary extravascular mass or leukaemia [16,183,204]. To date, canine IVLs have been derived primarily from T cells and non-T, non-B lymphocytes [183]. In a single case of IVL in a cat, the tumor was of T-cell origin [205]. Extraneural tumors cells sometimes localize in the meninges, e.g., meningeal carcinomatosis, often associated with an intestinal carcinoma or mammary adenocarcinoma [17,18].

**Meningiomas** - Meningiomas are extra-axial tumors that arise from dural elements within the cranial and spinal spaces. They are the most commonly reported brain tumors in cats [1,19] and one of the most common intracranial tumors in dogs, with a reported incidence in mature and immature dogs ranging from 30 to 39% [7-10,20]. In most reports, meningiomas occur in dogs over 7 years of age and in cats over 9 years of age, although meningiomas have also been observed in young cats (less than 3 years of age) with mucopolysaccharidosis type I [21], and in young dogs less than 6 months of age [8]. These tumors commonly occur in dolicocephalic breeds, especially German Shepherds [1,22]. Meningiomas in dogs and cats have estrogen, progesterone and androgen receptors [23] and usually are benign tumors (a high progesterone receptor expression may be correlated with a more benign tumor [176]) that tend to grow slowly under the dura mater, although in one canine study, there was direct invasion of the brain in 27% (6/22) of meningiomas [22]. They may be irregular, nodular, globular, ovoid, lobulated, or plaque-like masses ranging in size from a few millimeters to several centimeters in diameter. Meningiomas often are firm, rubbery, and encapsulated, and usually discrete. They can contain

granular calcifications known as psammoma bodies. Independently of these bodies, there can be focal or massive calcification of the tumor. A significant number of basal and plaque-like meningiomas involve the floor of the cranial cavity, especially in the optic chiasmal or suprasellar region [24]. They also occur commonly over the convexities of the cerebral hemispheres, less commonly in the cerebello-pontomedullary region, and infrequently in the retrobulbar space arising from the sheath of the optic nerve [1,22]. In cats, common locations include tela choroidea of the third ventricle and the supratentorial meninges. There is also a high incidence of multiple meningiomas in cats. Thickening of bone adjacent to meningiomas, termed hyperostosis, may occur, especially in cats [25]. Meningiomas may extend into paranasal regions, rarely metastasize outside the brain [26], and may occur as primary extracranial masses as a result of embryonic displacement of arachnoid cells or meningocytes [27]. These tumors differ from intracranial meningiomas mainly in their more anaplastic/malignant nature and aggressive behavior. In one study using CT scans, meningiomas were distinguished from tumors within the brain parenchyma because they usually were broad-based, peripherally located masses that were enhanced homogeneously with contrast material [7]. Cystic and edematous meningiomas have been detected using CT [28] and MRI [29]. When a "dural tail" (a linear enhancement of thickened dura mater adjacent to an extra-axial mass seen on Gd-DTPA-enhanced T1 weighted images) is seen using MRI, an associated mass is most likely a meningioma [30]. It is uncertain whether the dural tail represents neoplastic infiltration beyond the margins of the meningioma. The histologic types of meningioma in dogs include psammomatous, transitional, meningothelial or syncytial, fibroblastic, anaplastic (malignant) and angioblastic [4,27,179]. Microcystic/myxoid and papillary forms may also be seen [4,31,32]. In most instances, the tumors consist of large meningothelial cells or fusiform cells arranged in whorls, nests, and islands, or in stream-like patterns. Cell boundaries are typically ill-defined. Nuclei contain little chromatin. Canine meningiomas commonly express vimentin intermediate filaments [4]. More variable expression occurs with pancytokeratin, S100, and neuron-specific enolase (NSE), while glial fibrillary acidic protein (GFAP) expression has been observed in an anaplastic meningioma [179]. In this study of 15 meningiomas, synaptophysin was uniformly negative. Regressive changes may include hemorrhage, cavernous vascular formations, hyalinization of connective tissue, and deposits of fat, lipopigments, or cholesterol. Many have evidence of focal necrosis with suppuration [10], which probably accounts for the reported predominance of polymorphonuclear cells in CSF reported in many dogs with meningioma [33]. In cats, the majority of meningiomas are meningotheliomatous or psammomatous, often with cholesterol deposits [4].

Rarely, focal or diffuse sarcomas involve the meninges in dogs. With the latter, termed **meningeal sarcomatosis**, the meninges are diffusely thickened, often with extensive hemorrhages, and tumors (cell types include lymphoid, plasmacytoid, mature plasma cells, immunoblastic cells, and multinucleate giant cells [4] tend to infiltrate the nervous tissue and run along blood vessels [1]. Also very rare is the occurrence of meningiomas with granule cell component in dogs [34]. In this study, granular cells were oval to polygonal in shape and of various sizes. The cells had abundant, pale, eosinophilic cytoplasm with distinct intracytoplasmic granules, distinct cell margins, and mostly central nuclei, and reacted to the antibody S-100 protein.

### **Malignant Histiocytosis -**

Recently, focal and diffuse forms of CNS malignant histiocytosis (some reserve this term for disseminated histiocytic sarcomas) have been reported in dogs [172,173]. This seemingly rare condition is characterized by proliferation and/or infiltration of neoplastic histiocytes. In one report in which the condition was described as diffuse leptomeningeal malignant histiocytosis, there was moderate to severe infiltration of pleomorphic histiocytic mononuclear cells bilaterally in the basilarachnoidal and ventricular areas of the brain. The spinal dura mater, arachnoidal space, leptomeninges, and spinal nerve roots were also affected by infiltrative proliferation of these mononuclear cells. The infiltrating cells had the morphologic characteristics of histiocytes but exhibited moderate pleomorphism and numerous mitotic figures. Immunohistochemical studies revealed that most of the infiltrating cells were positive for lysozyme and lectin RCA-1 and negative for glial fibrillary acid protein, suggesting a monocytic/histiocytic-origin. Positive proliferating cell nuclear antigen immunostaining demonstrated that most nuclei of the histiocytic cells were in the S phase of the cell cycle, consistent with a proliferating population of cells. Ultrastructurally, the neoplastic cells have features of histiocytic cells with abundant lysosomes. The pathological features of malignant histiocytosis appear similar to those seen in the neoplastic form of granulomatous meningoencephalomyelitis (neoplastic reticulosis). It has been suggested that canine localized and disseminated histiocytic sarcomas are likely myeloid dendritic cell sarcomas [178].

**Astrocytomas** - Astrocytomas are probably the most common neuroectodermal brain tumors in dogs. In one study of neuroglial tumors in 215 dogs [10], 118 (55%) were benign or malignant astrocytomas. Eighty were located in the cerebrum, 20 in the brainstem, and 17 in the cerebellum. In one report of an 11 year old entire female German shepherd dog presented with a progressive non-painful exophthalmos, an anaplastic astrocytoma was found in a retrobulbar location, along with pulmonary metastases [35]. Astrocytomas consist of relatively large, protoplasmic-rich cells, or smaller cells with many processes. In most astrocytomas, there is a tendency for the cells to be arranged around blood vessels. Several

variants have been described, e.g., fibrillary, protoplasmic, pilocytic, anaplastic, and gemistocytic, most of which stain positively for glial fibrillary acidic protein (GFAP), the chemical subunit of the intracytoplasmic intermediate filaments of astrocytic cells [6]. Regressive changes include necrosis, mucinoid degeneration, cyst formation, vascular proliferation often in the form of glomeruloid nests, and multinucleated giant cells. Hemorrhage is very uncommon. Malignant astrocytomas are characterized by nuclear polymorphism, presence of mitotic figures, and small cells with dense, hyperchromatic nuclei [4]. An anaplastic astrocytoma involving the left optic nerve, optic chiasm, hypophysis and hypothalamic area was diagnosed in a 3.5 year old Boxer with progressive blindness of the left eye and was termed an 'optic chiasmatic-hypothalamic glioma' based on its unusual location and similarity to its human counterpart [175]. In one study using CT, astrocytomas were not distinguished easily from oligodendrogliomas because both tumors had similar features of ring-like and non-uniform enhancement, and poorly-defined tumor margins [7]. Distinguishing oligodendrogliomas from malignant astrocytomas with MRI has also been difficult [29], although MRI was considered superior to CT in defining diffuse leptomeningeal and cerebral low-grade astrocytoma in two dogs [36].

Astrocytomas are usually found in middle-aged or older dogs, but they have been reported in dogs less than 6 months of age [8]. They are common in brachycephalic breeds but can occur in any breed. Astrocytomas are very uncommon in cats [184]. In one report of four cats, the tumors invaded the third and lateral ventricles [37]. A mass with histological characteristics of a subependymal giant cell astrocytoma has been recently reported in a cat in which neoplastic cells were positive for S-100 protein, GFAP, and neuron-specific enolase and negative for neurofilament protein [185].

**Glioblastoma Multiforme** - Glioblastoma multiforme is a relatively common tumor in dogs and in one study represented 12% of 215 neuroglial tumors [10]. These tumors are considered to be "high-grade" gliomas, of diverse origin, including astroglial, oligodendroglial, and ependymal tissue [4]. Most are of considerable size and are most commonly located in the cerebrum. The tumor cells consist of medium sized, round or fusiform cells with isomorphic nuclei. Considerable pleomorphism has been noted in some tumors with small and large mononucleated and multinucleated cells [1,38]. Glioblastomas have an infiltrative, destructive growth. These are well vascularized and often contain necrotic zones. Glioblastomas may or may not express glial fibrillary acidic protein [6], although in a recent report of glioblastomas in 5 dogs, all tumors were GFAP positive, as well as positive for apoptosis and showed a proliferative index ranging from 12 - 25% [174]. MR characteristics include isointense to hypointense lesions on T1-weighted images that are hyperintense on T2-weighted images with prominent edema and mass effects, and sometimes ring enhancement [174]. The MRI and histological features have similarities to human glioblastomas. These tumors occur most commonly in brachycephalic breeds of dogs.

**Oligodendrogliomas** - Oligodendrogliomas are also common tumors in dogs (especially brachycephalic breeds), and in one report they comprised 28% of neuroectodermal tumors (54 oligodendrogliomas were located in the cerebrum, and 6 were found in the brainstem) [10]. In another review of 60 oligodendrogliomas, the neoplasm bordered on a ventricle or broke through the ependyma in more than half of the cases [1]. These tumors consist of densely packed, chromatin-rich, round cells with perinuclear halos. Most oligodendrogliomas grow by infiltration and destroy invaded tissue. Capillaries have a tendency to proliferate within these tumors, producing glomerulus-like structures. Regressive changes are similar to those in astrocytomas. Necrosis and extensive calcification are uncommon. These tumors do not stain with glial fibrillary acidic protein (GFAP); but in one study, three of 11 oligodendrogliomas reacted with myelin-associated glycoprotein [6]. None reacted with myelin basic protein. Many canine oligodendrogliomas are mixed tumors with areas of astrocytic, and sometimes ependymal, differentiation [4]. The MRI features are similar to those for high-grade (malignant) astrocytomas [29]. Oligodendrogliomas are rare in cats. In a recent report, oligodendrogliomas in 2 cats (one tumor was well differentiated; the other was an anaplastic subtype) occurred intraventricularly in the midbrain and fourth ventricle with aggressive intraparenchymal infiltration and extension into the basilar subarachnoid space of the midbrain and brain stem in one cat [195]. Immunostaining for several myelin- and oligodendroglia-specific antigens was negative. In both tumors, component cells of the intratumoral vascular proliferations were positive for human von Willebrand factor VIII antigen or smooth muscle actin. In both masses, GFAP staining identified both reactive astrocytes and a subpopulation of minigemistocytes. Prominent desmosomal junctions and paucity of microtubules were noted ultrastructurally.

**Medulloblastomas** - Medulloblastomas are uncommon, highly malignant neuroectodermal tumors in dogs that are almost exclusively located in the cerebellum [1]. The tumors often replace part of the cerebellar vermis, tend to bulge into the fourth ventricle, and may compress the midbrain rostrally and the brainstem ventrally. They may metastasize within the CSF pathways, cause obstructive hydrocephalus, and infiltrate the meninges. Microscopically, the tumor is characterized by sheets of densely packed cells with pale cytoplasm and oval or carrot-shaped nuclei that have coarse granulated chromatin. Mitotic figures are common. Regressive changes include pyknosis and karyorrhexis. While most cases involve young dogs, there is a recent report of a cerebellar medulloblastoma with multiple differentiation in a 4 year old Border Collie dog [39].

**Ependymomas** - Ependymomas are rare neuroglial tumors derived from the lining epithelium of the ventricles and central canal of the spinal cord and have been reported more frequently in brachycephalic breeds [1]. In one study, ependymomas represented only 2% of 215 neuroglial tumors, and three of the four ependymomas were noted in the third ventricle [10]. They are soft, gray to reddish, lobular masses with a propensity to invade the ventricular system and the meninges. Obstructive hydrocephalus may be a complication. Ependymomas of the fourth ventricle may grow out to girdle the brainstem. Metastases within the CSF system have been commonly observed [1]. Epithelial and fibrillary varieties have been described. Cells are isomorphic with pale or invisible cytoplasm and have round chromatin-rich nuclei. A characteristic feature is presence of nucleus-free zones around vessels. Some ependymomas appear hemorrhagic, and may show mucinoid degenerative changes and cyst formation. Malignant or anaplastic ependymomas show a moderate degree of pleomorphism and necrosis and may merge into glioblastoma multiforme [4]. In one study, only one of nine ependymomas was positive for glial fibrillary acidic protein [6]. In a computed tomographic study of brain tumors, there were no definitive distinguishing features identified with ependymomas [7].

**Choroid Plexus Papillomas** - Choroid plexus papillomas are common tumors in dogs with a reported frequency similar to that of glioblastomas (about 12% of neuroglial tumors). Approximately half of the 25 choroid plexus papillomas reported in one study [10] were located in the fourth ventricle, four were in the third ventricle, four were in lateral and third ventricles, and three were in the lateral ventricles. In another report of 16 tumors in dogs [40], their ventricular distribution was lateral and third ventricle (6 dogs each) and fourth ventricle (4 dogs). The choroid plexus epithelium originates from a differentiation of the primitive medullary epithelium and is related embryologically to the ependymal cells [40]. These tumors are reddish, papillary growths that have a tendency to bleed. Microscopically, choroid plexus papillomas are well defined, grow by expansion, and have a granular papillary appearance [1]. Tumor papillae consist of vascular stroma lined by one layer of cuboidal or cylindrical epithelium. These tumors have been classified as:

- a. choroid plexus papilloma (resembling normal choroid plexus and with low mitotic index),
- b. choroid plexus papilloma with atypical features (including increased cellular density, nuclear atypia, and 2 to 4 mitoses per 40x microscopic field, necrosis, and infiltration of the brain parenchyma, ventricular cavities/subarachnoid space, and/or leptomeninges, and
- c. choroid plexus carcinoma (characterized by marked nuclear atypia, poorly formed papillae, > 4 mitoses per 40x microscopic field, abnormal mitotic figures, and/or extraneural metastasis) [40,177].

In immunocytochemical studies of choroid plexus tumors in dogs [6,40], it was concluded that these tumors express epithelial but not glial differentiation, based on absence of staining with glial fibrillary acidic protein. Some tumors express keratin (pankeratin, cytokeratin AE1/AE3), and have positive vimentin immunoreactivity, occasional positivity for carcinoembryonic antigen, but are negative for epithelial membrane antigen, Ber EP4 and S-100 [40,177]. Exfoliation of choroid plexus papillomas (benign and malignant variants) may occur with subsequent dissemination to other areas of the brain or spinal cord via the CSF pathways. Obstructive hydrocephalus may be a complication. Extensive spread of the tumor in the subarachnoid space may lead to meningeal carcinomatosis [4,41]. When studied by CT, choroid plexus tumors were seen as well-defined, hyperdense masses that had marked, uniform contrast enhancement [7]. Strong enhancement is also seen with MRI, sometimes with hemorrhage and mineralization [29]. In one dog with choroid plexus carcinoma and meningeal carcinomatosis, multiple cyst-like structures were found in the parenchyma of the cerebrum, cerebellum and brainstem using MRI [42]. Choroid plexus papillomas have no apparent predilection for brachycephalic breeds. They are rare in cats.

**Gangliocytomas** - Gangliocytomas are rare intracranial tumors that have been described in mature dogs of several breeds [1]. Microscopic features often include mature, neuronal-like cells with multiple processes, a central nucleus and a nucleolus. Neuroblastlike immature cells may also be seen, and occasionally, newly formed myelin sheaths. These tumors appear to have a predilection for the cerebellum. Pure gangliocytomas have no glial elements and do not express glial fibrillary acidic protein [43]. Mineralization and extensive necrotic areas accompanied by edema and variable capillary proliferation have been observed in some cases.

**Pituitary Tumors** - Pituitary tumors are common in dogs but infrequently seen in cats. In one review, approximately 50% of the canine pituitary adenomas occurred in brachycephalic breeds [1]. They may be non-functional or functional. Although it is uncommon, tumors of either type are capable of causing hypopituitarism by mechanical or functional impairment of remaining pituitary tissue. Nonfunctional pituitary tumors occur often in dogs and are usually chromophobe adenomas,

although non-functional pituitary adenocarcinomas have been reported [44]. Functional pituitary tumors associated with the adeno-hypophysis are typically characterized by pituitary-dependent hyperadrenocorticism (PDH). Eighty percent or more of cases of pituitary Cushing's disease are reportedly associated with a pituitary tumor [45]. In dogs, these tumors may stem from the pars distalis (80%) or the pars intermedia (20%) since both regions contain cells that are capable of producing adrenocorticotrophic hormone (ACTH). The tumors are usually chromophobic microadenomas (< 1 cm in diameter) that do not produce neurological signs. Results of MRI suggest that up to 60% of PDH dogs without neurological signs have pituitary tumors 4 to 12 mm in diameter (at greatest vertical height). It has also been stated that up to 50% of dogs with PDH have large chromophobic macroadenomas (> 1 cm in diameter) and some of these dogs do not manifest clinical signs of an intracranial mass [46,47]. It has been estimated that at least 15 to 20% of all dogs with PDH will develop clinical problems due to a growing pituitary tumor during the first 2 or 3 years after diagnosis [48,49]. In one study, seven of eight dogs with pituitary gland neoplasms (2x malignant pituitary adenocarcinomas and 5x pituitary adenomas) that had been treated for PDH for varying periods of time (from 1 to 2 years), developed neurological signs, including behavior abnormalities (such as pacing, lethargy, wandering, hiding, tight circling, head pressing, and trembling), seizures, and positional nystagmus [50]. As most pituitary tumors, especially those derived from the pars distalis (chromophobe tumors in dogs from the pars intermedia are smaller and less destructive [4]), tend to grow dorsocaudally because of an incomplete diaphragma sellae [1], dorsal extension of pituitary tumors may lead to compression and obliteration of the infundibulum, ventral aspects of the third ventricle, hypothalamus and thalamus, and eventually impinge on internal capsules and optic tracts [4]. Involvement of the hypothalamus and median eminence may result in central diabetes insipidus [51], particularly in middle-aged and older dogs with neurological signs as well as polyuria, polydipsia, and isosthenuria or hyposthenuria [136]. Disturbance of water balance is the result of interference with the synthesis of antidiuretic hormone in the supraoptic nucleus or release of the hormone into capillaries of the pars nervosa [45]. While visual impairment is reportedly infrequent with pituitary tumors, acute blindness and dilated non-responsive pupils have been observed in seven dogs and one cat with pituitary masses that caused optic chiasmal compression [44]. According to Feldman [49], approximately 80% of cats in his practice diagnosed with Cushing's disease had PDH, and tumors included pituitary microadenomas, macroadenomas, and adenocarcinomas. Pituitary acidophil adenomas, especially the large variety, have been associated with acromegaly and nervous system signs (such as circling and seizures) in cats, accompanied by insulin-resistant diabetes mellitus and high serum growth hormone concentrations [52]. In pituitary tumors, polygonal, round, and cylindrical cells are arranged in close contact to blood vessels or form islands of cells divided into compartments by connective tissue [1]. The cell pattern may be monotonous and resemble normal pituitary gland tissue. Many pituitary tumors contain both chromophobe and chromophil cells. Regressive changes include necrosis, cyst formation, and hemorrhage. Chromophobe carcinomas are infrequent and usually separated from adenomas on the basis of invasion along the base of the brain into the sphenoid bone, since nuclear pleomorphism and mitotic index may be similar to those seen in adenomas [4]. MRI is an extremely useful aid for visualizing the presence of microtumors (3 to 10 mm in diameter) and macrotumors (up to 24 mm) in dogs with PDH, with or without neurological signs [46,48], especially when it is considered that there is no significant difference in endocrine test results when comparing dogs with a visible pituitary mass to dogs without [53]. Tumors are better visualized with contrast enhancement [48]. MRI and CT scans of pituitary tumors have revealed minimal peritumoral edema, uniform contrast enhancement, and well-defined margins [7,29]. Pituitary tumors less than 3 mm in diameter may not be visible with MRI or CT [47]. Note that pituitary and adrenal tumors can coexist in dogs with hyperadrenocorticism, resulting in a confusing mixture of test results that may complicate diagnosis and treatment of hyperadrenocorticism [54].

**Suprasellar Germ Cell Tumors** - Suprasellar germ cell tumors, located at the base of the brain above the sella turcica, are rare developmental tumors that are often intimately associated with the pituitary gland that may be trapped within or replaced by the germ cell tumor [55-57]. These tumors are thought to result from extensive migration of germ cells during embryogenesis. Neurological signs may be acute in onset and include lethargy or depression, bradycardia, dilated non-responsive pupils, ptosis, and visual deficits or blindness. Germ cell tumors can be quite large, extending from the olfactory peduncles to the pons and pyriform lobes [4], and can envelope other cranial nerves (e.g., III through VII). Microscopically, the tumors usually contain a mixture of primitive germ cells, cords resembling hepatocytes, and acini and tubules of tall columnar epithelial cells. They may stain positively for alpha-fetoprotein. Affected animals are usually 3 to 5 years of age and Doberman Pinschers may be at risk. The tumor has been reported in a 5 year-old Rottweiler [55]. Some germ cell tumors have been misdiagnosed as pituitary tumors and craniopharyngiomas [4].

**Malformation Tumors** - Malformation tumors, such as epidermoid and dermoid cysts, teratomas, and teratoids, are rare neoplasms in dogs that originate from heterotopic tissue. These tumors usually lie close to embryonal lines of closure.

**Epidermoid and Dermoid Cysts** - Result from inclusion of epithelial components of embryonal tissue at the time of closure of the neural tube. Those that have been reported have a predilection for young dogs (e.g., from 3 months to 2 years of age), although cysts have been seen in older dogs, and typically involve the cerebello-pontine angle, fourth ventricle, or both [1,58,59]. Cysts within the fourth ventricle may produce secondary compression of the medulla oblongata and the cerebellum. A cerebellar epidermoid cyst has been reported in a 7 year-old Pitbull with signs of progressive disequilibrium [60]. Cerebellar and medullary dermoid cysts have been recently reported in 7 year-old dogs. In one dog, a 1.6 x 0.8 x 1.5 cm, thinly encapsulated mass was found on the left cerebellar peduncle. It had caused dorsal displacement of the left portion of the cerebellum and ventral compression of the fourth ventricle [59]. In the other dog, MRI revealed the medullary cyst and secondary hydrocephalus. There was little edema associated with this lesion and no enhancement with gadolinium [61]. Some epidermoid cysts are found as incidental findings at necropsy [58,62]. Epidermoid cysts may have a multilocular structure and are typically lined by stratified squamous epithelium and contain keratinaceous debris, desquamated epithelial cells, and occasional inflammatory cells; whereas, dermoid cysts contain adnexal structures such as hair follicles, sebaceous glands, and sweat glands. Cysts may measure up to 2.5 cm in diameter. Because of their location, dogs may show signs of a pontomedullary syndrome (including trigeminal, facial, cerebellar, and/or vestibular dysfunction). A dermoid cyst and an intracranial teratoma, both approximately 1 cm in diameter, were found in a 4 month old kitten [135] located in the ventral forebrain protruding into the lateral ventricle. The teratoma was grossly mottled tan-gray and multilobulated with small cysts and markedly compressed the 3rd ventricle. It was located close to the thalamus and hypothalamus, adjacent to the pituitary stalk. Microscopically the mass was composed of myriad structures including collagenous stroma, striated muscle cells, melanocytes, adipose tissue, dilated tubules lined by cuboidal-columnar-pseudostratified epithelium containing goblet cells, and exocrine pancreatic cells forming acini. Teratomas represent well-differentiated germ cell tumors (see above) arising from several embryonic germ cell layers.

**Intracranial intra-arachnoid Cysts** - Have also been described in dogs [63,202,203]. These rare malformation tumors (see also spinal arachnoid cysts) appear to have a predilection for the quadrigeminal cistern. The cysts are often found in small breed dogs of either sex, and occur in both immature and adult dogs. Other developmental anomalies (e.g., abnormal corpus callosum and block vertebrae) may be detected. The cysts, on MRI and CT scans, are extra-axial and have sharply defined margins, and contain fluid usually iso- or hypointense to CSF (in T2-weighted images). In some instances, intracystic hemorrhage has been demonstrated [203]. Ultrasonographic images are characterized by well-defined, oval to triangular-shaped anechoic area between the caudal aspect of the occipital lobes, dorsal to the midbrain, and rostral to the cerebellum [202].

**Hamartomas** - Are focal malformations that resemble neoplasms and are formed by disorderly overgrowth of tissue elements normally present at that site [4]. Hypothalamic hamartomas have been reported only rarely in dogs and usually as subclinical entities [64]. However, a 10 month old Wire-haired Pointing Griffon dog had a hamartoma of the hypothalamus and manifested episodes of sudden flaccid collapse that increased in frequency and duration for 7 months [65]. Cerebrospinal fluid pressure was normal. A flat, pedunculated mass, 2.5 X 3.0 X 1 cm, covered the brain stem between the pituitary gland and pons. Its 1.2 cm diameter connection to the hypothalamus obliterated the mammillary bodies and extended to the tuber cinereum, distorting the hypothalamus and displacing the third ventricle, which also divided the rostral part of the mass. The tissue of the hamartoma resembled gray matter with bullous cytoplasmic vacuolation of many neurons, spongiform change, gemistocytosis and microscopic foci of calcification. Vascular malformations are also uncommon in dogs and cats and are considered developmental lesions rather than true neoplasms [4]. Fankhauser and colleagues reported the occurrence of vascular malformations (telangiectatic hamartomas and cavernous hemangiomas) in 11 dogs aged from 6 to 17 years [66]. Locations were the cingular gyrus (3 dogs), piriform-hippocampal area of the temporal lobe (3 dogs), basal ganglia (2 dogs), septum pellucidum and fornix (1 dog), occipital lobe (1 dog) and cerebellum (1 dog). The hamartomatous structures consisted of accumulations of vessels (arteries, veins, and capillaries, either alone or in combination). The anomalous vessels tended to be dilated and had a sinusoidal shape, and were often accompanied by hemorrhages. These authors also observed a large cavernous angioma in the cerebral hemisphere of a cat. A large vascular hamartoma (possibly a cavernous angioma), located in the septal area and thalamus, has been noted in a 13 year-old Poodle [4]. In a recent report, vascular hamartomas from the brains of five dogs were characterized using histochemistry and immunohistochemistry [67]. All five hamartomas were located in the telencephalon, three in the pyriform lobe, without any predilection for the left or right side. Each hamartoma consisted of a proliferation of thin-walled vessels that varied in caliber. These vessels were elastin-negative, with varying amounts of collagen and no muscular component. In four of the five hamartomas, lining cells were actin- and factor VIII-positive. All five hamartomas contained glial fibrillary acid protein (GFAP)-positive parenchyma at moderate to high frequency, and four contained neurofilament-positive axons between component vessels. Meningioangiomatosis, a rare benign malformation of the vasculature of the central nervous system, characterized by the proliferation of blood vessels and spindle-shaped, perivascular meningotheial cells has been described in the cerebral cortex

and brainstem of immature and mature dogs [4]. The meningotheial cells stain positively for vimentin [68,69], which, together with presence of collagen and mucopolysaccharides among proliferating cells, suggests a mesenchymal and fibroblastic origin of these cells [69]. A hematoma located in the parietal portion of the right cerebral hemisphere surrounded by numerous thin-walled veins, considered to be a venous malformation, has been reported in a 14 year-old dog [70].

**Primary skeletal tumors** - Primary skeletal tumors infrequently result in neurological signs. Multilobular osteochondroma occurs as a firm, fixed mass originating from the flat bones of the skull, usually in older medium-to large-breed dogs [71,193]. The tumor can erode the cranium and compress, rather than infiltrate, underlying brain tissues. Radiographically, the tumor contains nodular or stippled mineralized densities resulting in a characteristic ‘popcorn ball’ appearance. Microscopically, the tumor is characterized by multiple lobules of osseous and chondroid tissue. Local tumor recurrence and metastasis are common. The spinal cord counterpart is the vertebral osteochondroma (see osteochondromatosis). An extremely rare primary intracranial malignant plasma cell tumor has been reported in a 5 year old female spayed Spitz dog with a 5-week history of right head tilt, seizures, and progressive quadriplegia [72]. Analysis of cerebrospinal fluid revealed 27,600 white blood cells per  $\mu$ l with 63% mononuclear phagocytes, 27% lymphocytes, 6% neutrophils, 3% plasmacytoid cells, and 1% eosinophils, and over 2000 mg/dl protein. On contrast-enhanced magnetic resonance images, a focal 1 cm oval lesion was identified in the right ventral brainstem. There was also marked contrast enhancement of the meninges in the following areas: surrounding the brainstem, outlining cerebellar folia, along the ventral floor of the brain and extending to the falx cerebri, and partially outlining the left frontal lobe. At necropsy, the areas of contrast enhancement corresponded to the presence of compact cellular sheets of pleomorphic, anisocytotic, oval to polygonal neoplastic cells with plasmacytoid differentiation. The smaller of these plasmacytoid cells stained predominantly for cytoplasmic immunoglobulin A using immunoperoxidase methodology. Ultrastructurally, the neoplastic cells had morphologic features typical of plasma cells, with large amounts of predominantly rough endoplasmic reticulum with variably prominent Golgi formation.

### Clinical Signs of Brain Tumors

Some of the clinical signs/syndromes associated with specific intracranial CNS tumors have already been mentioned. According to tumor location, one might anticipate cerebral, hypothalamic/diencephalic, midbrain, cerebellar, pontomedullary, and vestibular syndromes associated with focal discrete intracranial masses. In many cases, accurate anatomic diagnosis (localization) is possible, especially in the early stages of tumor growth. However, in some intracranial tumors, accurate clinicopathological correlations are frequently impossible [73]. This is because the actual location of a tumor may be masked by secondary changes such as cerebral edema, hemorrhage, obstructive hydrocephalus, brain herniations, tissue necrosis, and tumor spread within the brain [4], all of which may result in clinical manifestations in their own right. Usually as a consequence of increased intracranial pressure and/or shifts in parts of the brain as a result of the mass lesion, herniation of portions of the brain may ensue. Several types of herniation have been described in dogs [4,74]:

- a. The cingulate gyrus herniates under the falx cerebri toward the unaffected hemisphere, leading to compression of the opposite cingulate gyrus. Interestingly, clinical signs attributable to this form of herniation were not identified in one report [74].
- b. The occipital or temporal lobe (mainly the parahippocampal gyrus) herniates under the tentorium cerebelli (caudal transtentorial herniation). This often causes dorsoventral and lateral compression of the midbrain at the rostral colliculi and partial occlusion of the mesencephalic aqueduct. There may also be caudal displacement of the diencephalon and midbrain. Clinical signs include pupillary constriction (initially) often followed by mydriasis, tetraplegia and coma.
- c. The rostral cerebellar vermis herniates under the tentorium cerebelli (rostral transtentorial herniation) which may lead to flattening of the rostral cerebellum, compression of the temporal cortex, and marked compression and rostral displacement of the brainstem. Despite the gross pathology occurring with this form of herniation, clinical deficits may not be seen [74].
- d. The cerebellum (especially the caudal lobe of the cerebellar vermis) herniates through the foramen magnum. The herniated portion is flattened and may be malacic and hemorrhagic, and compresses the underlying medulla oblongata. Clinical signs may include apnea, hypoxia-induced coma, and tetraplegia. Concurrent foramen magnum and caudal transtentorial herniation has been reported leading to signs of both midbrain and medulla oblongata dysfunction [74].



Herniation combined with attenuation of the ventricular system, especially at the level of the mesencephalic aqueduct, can lead to obstructive hydrocephalus and elevated intracranial pressure, and ischemic necrosis of the herniated tissue can result [75]. An additional clinicopathological caveat is that as many as 50% of cats with meningiomas do not manifest clinical signs [21,76].

Initial abnormalities associated with tumors involving the rostral cerebrum (e.g., olfactory and frontal lobes) may be restricted to seizures and behavioral changes [77]. Lesions in frontal and prefrontal lobes of the brain may be clinically silent [9]. Acute blindness may be the initial presenting clinical sign in animals with tumors in the region of the optic chiasma, e.g., pituitary tumors, paranasal sinus carcinoma, polycentric lymphosarcoma, and suprasellar germ cell tumors [44,57]. Presence of papilledema (often bilateral) has been reported in dogs with brain tumors and is considered to arise from generalized increase in intracranial pressure [73]. Clinical signs of a multifocal syndrome may occur in animals from a variety of causes. This syndrome may result from multiple small metastatic masses from extracranial tumors, especially with malignant melanoma and hemangiosarcoma [4,78]. Other tumors, such as carcinomas (pulmonary, mammary) tend to produce fewer, larger metastases [4]. Some hematogenous metastases appear to have a propensity for gray matter, commonly in the cerebrum, hippocampus, and cerebellar cortex [4,78]. Extraneural tumors cells sometimes localize in the meninges, e.g., meningeal carcinomatosis associated with an intestinal carcinoma or mammary adenocarcinoma [17,18]. Metastases to the meninges and/or choroid plexuses often occur in dogs and cats with multicentric lymphoma [4,15,79]. A multifocal syndrome may also occur with primary CNS tumors having multiple sites (meningiomas in cats are often multiple [1]), from spread of the original tumor to another site by extension (e.g., astrocytoma, glioblastoma) or through metastases via the CSF pathways (e.g., medulloblastoma, choroid plexus papilloma, and ependymoma) [73]. Because of their ventricular orientation, ependymomas and choroid plexus papillomas have a tendency to obstruct cerebrospinal pathways, particularly when they arise in the fourth ventricle. Accordingly, neurological signs associated with ventricular tumors will reflect tumor localization and varying degrees of ventricular dilatation resulting from obstructive hydrocephalus. With either of these tumors, clinical signs are often insidious and the clinical course is usually protracted, ranging from months to years. Extraneural immunoproliferative diseases in dogs and cats [80,81], such as macroglobulinemia-associated lymphocytic leukemia and multiple myeloma, can also produce a spectrum of intermittent cranial neurological abnormalities (including disorientation, ataxia, intention tremor of the head, possible visual impairment, occasional circling, and staggering/falling) as a result of serum hyperviscosity - the transient signs probably result from impaired blood flow in the vascular beds of affected areas due to increased intravascular erythrocyte aggregation [81].

Various endocrine signs can be associated with pituitary tumors, including polydipsia, polyuria, obesity, gonadal atrophy, abnormal hair coat, and acromegaly. Recently, a condition termed "pituitary apoplexy" was described in a 7 year-old German Shorthaired Pointer with a pituitary adenoma and associated hemorrhages [82]. Signs included polydipsia, polyuria, acute vomiting and collapse followed by development of convulsions and hyperthermia, and a shift from bilateral pupillary miosis to mydriasis. The dog also had evidence of hyponatremia. A rare condition termed "diencephalic syndrome" was described in a 3 year-old Doberman Pinscher associated with an astrocytoma located in the rostral hypothalamus [83]. The dominant clinical sign was chronic weight loss, followed by hypothermia with lack of a shiver response, lack of thirst despite negative water balance, and persistently low-normal heart rate. The only neurological abnormality noted was circling.

Extension of primary nasal cavity tumors into the cranial vault may lead to seizures, behavior changes, paresis, circling, and visual deficits [9,84]. Respiratory signs such as sneezing, nasal discharge, epistaxis, stertor, dyspnea, and mouth breathing may develop after neurological signs, or may not be seen at all.

## **Spinal Cord Tumors**

**Overview** - Spinal cord tumors are relatively common in dogs and cats and are usually classified according to their position with respect to the spinal cord and meninges as either extradural, intradural-extramedullary, or intramedullary tumors [85]. According to tumor location, any of the four spinal cord syndromes can be anticipated (see cervical syndrome, cervicothoracic syndrome, thoracolumbar syndrome, and lumbosacral syndrome). Most dogs with spinal tumors, regardless of type, have a mean age around 6 years of age [86-88]. Cats with lymphosarcoma tend to be younger, having a mean age of approximately 3.5 years [89], possibly related to the infectious etiology of most cases (i.e. feline leukemia virus). However, age alone does not preclude a diagnosis of spinal tumor. In one study of spinal tumors in dogs, 8 of 29 animals (30%) were 3 years of age or less [90]. In that study, approximately 90% of the spinal tumors occurred in medium and larger canine breeds. The clinical course is still not clearly defined for tumor types and their location. In one study, the rate of progression was fastest with intramedullary tumors (1.7 weeks), followed by extradural tumors (3.4 weeks), and intradural-extramedullary tumors (5.7 weeks) [90].

**Extradural Tumors** - Extradural tumors are located outside the dura mater and result in spinal cord compression. Extradural tumors are the most common spinal tumors in dogs and cats. The most frequently occurring types of canine spinal cord tumors are primary, malignant bone tumors (osteochondromas or multiple cartilaginous exostoses, osteosarcoma, chondrosarcoma, fibrosarcoma, hemangiosarcoma, hemangioendothelioma, and multiple myeloma), and tumors metastatic to bone and soft tissue [1,86,91,92]. Secondary tumors of the vertebrae of the dog that have been reported include mammary carcinoma, prostatic carcinoma, anaplastic tumors, transitional cell carcinoma, osteosarcoma, thyroid carcinoma, perianal gland carcinoma, chemodectoma, ganglioneuroma, fibrosarcoma, bronchogenic carcinoma, tonsillar carcinoma, hemangiosarcoma, Sertoli cell carcinoma, lymphosarcoma, rhabdomyosarcoma, pancreatic adenocarcinoma, malignant melanoma, squamous cell carcinoma, and aortic body tumors [1]. An extradural ganglioneuroma and its undifferentiated counterpart, ganglioblastoma, have been reported in dogs [93,94]. Primary vertebral tumors are rare in the cat, with osteosarcoma being most commonly reported. Metastatic extradural tumors affecting the spinal cord are unusual in dogs, e.g., uveal melanoma [208]; however, extradural lymphosarcomas are the most common feline spinal tumors [19,89]. In most instances, these tumors are secondary to lymphosarcoma elsewhere in the body, although primary spinal cord lymphosarcoma has been reported sporadically in dogs [15,95]. In a study of spinal lymphosarcoma in 23 cats, the absence of detectable extraneural involvement was noted in approximately 50% of cats [89]. The tumors were solitary in 22 of the cats and there was an apparent predilection for the thoracic and lumbar vertebral canal; however, they may occur in any spinal region [19]. Three of the tumors involved the cervical roots of the brachial plexus (see peripheral nerve tumors). Spinal lymphomas in cats may extend over multiple vertebral bodies, and there may be more than 1 level of spinal cord involvement [96]. In contrast with intracranial lymphoma, leptomeningeal spinal cord involvement is not common in cats. At least some of these tumors are large granular lymphocyte lymphomas [181]. Recently, an extradural spinal liposarcoma was described in an 8 year old female Doberman Pinscher [97]. It was not determined if this was a primary tumor. A tumor termed myxoma-myxosarcoma has been described for the first time in 4 dogs [98]. These malignant tumors resemble soft tissue myxomas in that the cells were polygonally shaped with gray and vacuolated cytoplasm and stained positive for S-100 protein antibody. The masses were reported as being extradural in 3 cases and intradural-extramedullary in the fourth dog. A primary extracutaneous mast cell tumor compressing the spinal cord at the level of the sixth cervical to first thoracic (C6 - T1) vertebrae was reported in a 6 year old Rottweiler [192].

**Intradural-extramedullary Tumors** - Intradural-extramedullary tumors are located in the subarachnoid space. Intradural-extramedullary tumors are usually represented by meningiomas and nerve sheath tumors (e.g., neurofibromas, neurilemmomas, and schwannomas) that grow into the vertebral canal and compress the spinal cord [86,90,94]. It has been estimated that intradural-extramedullary tumors represent approximately 35% of all spinal cord tumors [85,86]. About 14% of CNS meningiomas reportedly involve the spinal cord in dogs [10] (27% in the cervical spinal cord, 47% in the thoracic cord, and 27% in the lumbar cord), whereas in cats, only 4% of all CNS meningiomas reportedly occur in the spinal cord [99]. In another study of spinal meningiomas in 13 dogs, 10 were located in the cervical region and three were found in the lumbar area [100]. Four of these meningiomas invaded the spinal cord. In a report of spinal cord tumors in 29 dogs, nerve sheath tumors were the second most common tumor (vertebral tumors were the most common) [86]. In another review of spinal tumors in dogs, 39 of 60 nerve sheath tumors involved the spinal cord [10]. Nerve sheath tumors are commonly associated with the brachial plexus (see peripheral nerve tumors). An unusual intradural-extramedullary lipoma has been reported in a 4 year-old, female mixed-breed dog that was presented for chronic, persistent lumbar pain, episodic urinary incontinence, fecal incontinence, and weak anal sphincter tone [101]. Due to congenital absence of a tail, the presence of eight lumbar vertebrae, and a dimpled area in the lumbosacral region, the lipoma was suspected to have a developmental origin. Summers and colleagues consider these tumors to be malformative or hamartomatous [4] (see hamartoma). A primary intradural-extramedullary tumor that has a predilection for T10 to L2 spinal cord segments in young dogs, especially German Shepherds and Retrievers, has been variously diagnosed as ependymoma, medulloepithelioma, neuroepithelioma, and **nephroblastoma** [86,90,102]. The origin of this tumor is presently unknown; immunocytochemical studies have not supported a neuroectodermal origin as staining for neuroectodermal antigens (e.g., GFAP, neurofilament, and neuron-specific enolase) is negative; however, monoclonal antibody studies support the nephroblastoma claim [4]. Most affected dogs are between 5 and 36 months of age. There is no gender predilection. Clinical signs are characterized by a thoracolumbar syndrome. Analysis of CSF is usually normal, although an elevated protein level has been documented in one dog. The extramedullary masses are tan to grayish-white in color and may measure from 1 to 3 cm in length. The masses are usually located dorsal and lateral to the spinal cord and may entrap the spinal roots. Some have areas of hemorrhage. The spinal cord may be severely compressed. Microscopic findings include solid sheets of ovoid to fusiform cells interspersed with areas of acinar and tubular differentiation, focal squamous metaplasia, and rudimentary glomeruli [4,102]. Recently, multifocal or possible intraspinal metastasis of a canine spinal cord nephroblastoma was reported in a 2 year old Basset Hound [137].

**Intramedullary Tumors** - Intramedullary tumors are the least common of the three categories of spinal cord tumors - a frequency of 15 to 24% has been reported [85,90,103]. This group is largely represented by primary glial tumors (e.g., astrocytoma, oligodendroglioma, undifferentiated sarcoma, ependymoma, and choroid plexus papilloma). In one report of an anaplastic astrocytoma in a 9 year old cat, areas of the lumbar spinal cord were flattened and contained a dorsal cleft [186]. Intramedullary spinal cord metastasis (ISCM) is an uncommon complication of systemic malignancy. This condition has been described in dogs [14,85]. There is no evidence of tumor metastasis in the epidural space or in vertebral bone. Intramedullary involvement may consist of large space-occupying masses or micrometastases in the absence of gross tumor. In dogs, hemangiosarcoma and lymphosarcoma have a propensity for intramedullary spinal cord involvement, but mammary gland adenocarcinoma, malignant melanoma, and bronchoalveolar carcinoma are also occasionally observed [14,104]. Neurological signs in animals with ISCM may be the first clinical manifestation of systemic malignancy. The mean age of affected dogs is around 6 years, and any area of the spinal cord may be affected. Brain metastasis may accompany ISCM. Spinal cord malignancy associated with granulomatous meningoencephalomyelitis is reported sporadically. Malformation tumors affecting the spinal cord are rare. An intramedullary epidermoid cyst has been reported in a 2 year-old, female Rottweiler presented with a thoracolumbar syndrome [105]. A gray to pearl-colored intramedullary cyst approximately 2 cm long and 1 cm in diameter extended from T13 to L1 spinal cord segments. The empty lumen was lined by simple stratified squamous epithelium or, less frequently, by desquamating keratinized epithelium, containing keratohyaline granules. The spinal cord was severely compressed. These cysts may arise from growth of primordial epithelial cells entrapped during closure of the neural tube (see also arachnoid cysts). A caudal lumbar intramedullary chordoma has been reported in a 4 year old Labrador Retriever [196]. Histologically there were variable sized cells that were stellate in appearance with vacuolated cytoplasm (physaliferous cells) and mucinous background. Chordomas originate from remnants of the embryonal notochord. An intramedullary spinal cord hamartoma was recently identified in a 9 year old Golden Retriever [201].

### **Peripheral Nerve Tumors**

Tumors of cranial and spinal nerves and nerve roots are common in dogs [10]. In one study, peripheral nerve tumors represented approximately 27% of canine nervous system tumors [106]. The terminology given to these tumors has been confusing because of differing opinion regarding their cell of origin. Although "schwannoma", "neurilemmoma", and "neurofibroma" are accepted and used interchangeably, the designation "malignant peripheral nerve sheath tumors" (MPNST) is recommended [4], especially since many of these tumors are malignant (based on cytological criteria such as anaplasia, high mitotic index and necrosis, or invasive biological tendencies, including spinal cord invasion) and determining the cell of origin (e.g., Schwann cell, perineurial cell, fibroblast, etc) is usually impossible [4]. Microscopic findings of MPNSTs often include dense fascicles of Schwann cells and/or fibroblasts with elongated nuclei, as well as cells with anaplastic features, imbedded in dense connective tissue. There may be evidence of myelinated axons. Schwannomas may be characterized by spindle-shaped cells exhibiting band-like herringbone or palisading patterns (Antoni A tissue) and spindle or oval cells arranged randomly within a loose matrix, often with extensive regressive changes (Antoni B tissue) [10]. Varying patterns of differentiation, such as cartilage, bone, squamous epithelium with keratinization, epithelial/glandular components, and rhabdomyoblastic features have been reported [4,107,200]. Rare variants, as malignant melanotic schwannomas have been seen in dogs [108]. Immunohistochemical studies have shown that tumor cells in schwannomas (neurinomas) were positive for S-100 antigen, while neurofibroma cells were negative [107]. A recent report suggests that expression of a point mutation of the neu oncogene could be a useful diagnostic genetic marker in MPNSTs [198].

MPNSTs most commonly involve mid to low cervical and/or rostral thoracic nerve roots, especially ventral roots [86,109], or more peripherally-located single nerves in which the tumor may advance distally or proximally. Dorsal root involvement has also been noted and may be associated with ill-defined cervical pain [110]. MPNSTs less commonly affect thoracolumbar and lumbosacral roots [88,111,200]. Tumors frequently involve nerves of the brachial plexus, often appearing as bulbous or fusiform thickenings of one or more nerves [4], and are capable of spreading to other nerves once they advance to the area of the common brachial plexus bundle [85,86,88]. The tumors typically result in slow, progressive unilateral thoracic limb lameness and muscle atrophy, often involving the infraspinatus and supraspinatus muscles. Affected animals may have a unilateral Horner's syndrome, there may be pain on leg movement or axillary pain on palpation, a palpable axillary mass may be found, and the animal may be licking or chewing at the foot or carpus of the affected limb [87,88,109]. It should be noted that dogs might present with acute onset of signs associated with spinal cord compression without showing any forelimb signs [87]. Tumors at the level of the spinal nerve roots are usually those involved with intradural-extramedullary spinal cord compression, although the more peripherally-located tumors can also sometimes invade the vertebral canal from without [88]. Wright reported that all 9 brachial plexus tumors in her study involved the spinal cord [86], while other have observed a lower incidence [109]. Bradley and colleagues reported 10 of 15 cases were myelographically positive for an intramedullary-extramedullary lesion [88]. In one study, pelvic limb signs were not seen in 50% of dogs with cervical MPNSTs with evidence of intradural extramedullary involvement, suggesting slow rate of growth

and spinal cord compensation [88]. In contrast, in the same study, MPNSTs found in the thoracolumbar region were always intradural and all produced cord compression and or invasion of the cord parenchyma [88]. Of the cranial nerves, MPNSTs commonly involve the trigeminal nerve producing signs of unilateral trigeminal nerve dysfunction (e.g., unilateral temporalis and masseter muscle atrophy) [112]. Brain stem compression from a neurofibroma thought to be of cranial nerve origin, and from a trigeminal neurofibrosarcoma/schwannoma, has been reported in dogs [113,180]. An intrathoracic MPNST believed to originate from ventral nerve roots has been identified in a dog [187]. A large MPNST was detected in the ventral cervical region of an eight year old Bernese mountain dog, originating from the right vagosympathetic trunk [197]. Clinical findings included Horner's syndrome, ipsilateral laryngeal hemiplegia, coughing, gagging, respiratory distress and vomiting. Note that local vertebral erosion is occasionally reported in dogs with MPNSTs [86]. Peripheral nerve sheath tumors are rare in cats but there have been reports of tumors producing spinal cord compression at T4 and T12 - L1 vertebral levels [4,19]. Vertebral body erosion occurred in one report [4]. In a recent report, a soft tissue MPNST that invaded the occipital and temporal bones of the skull was reported in a 9 year old cat. The tumor was diffusely positive for S-100 protein and scattered cells stained intensely for GFAP.

Other tumor types may also involve peripheral nerves. A giant cell sarcoma was reported in one dog with a suspected cervical MPNST, along with local vertebral erosion [86]. Two sarcomas and a malignant tumor of the apocrine sweat glands extending into the brachial plexus were reported in dogs [109]. Peripheral tumors of neuronal origin, such as ganglioneuromas and their more undifferentiated counterparts, ganglioneuroblastomas, resulting in neurological signs, appear to be extremely rare, but extradural spinal cord compression has been reported in dogs [93,94]. In one report of a ganglioneuroma extending into the nerve root sheaths, the tumor consisted of a diffuse population of neuronal cells with distinctive Nissl substance, round vesicular nuclei and prominent nucleoli, distributed in a background of nerve fibers and fibrous connective tissue [93]. Ganglioneuromas are thought to be derived from sympathetic ganglia [4]. Lymphosarcoma occasionally involves cranial and spinal nerves and nerve roots in dogs and cats, and may extend intracranially [19,89,114,138]. Myelomonocytic neoplasia of the trigeminal nerves and ganglia, resulting in dropped mandible and symmetrical atrophy of masticatory muscles, has been reported in dogs [115,116]. In these cases, neoplastic blast cells also infiltrated multiple cranial and spinal nerves. Other signs may include Horner's syndrome, loss of corneal sensation, diminished palpebral reflex, decreased sensation of the nasal mucosa, tongue paralysis, and hind limb weakness/paralysis. Various tumors of the ear canal, such as squamous cell carcinoma, ceruminous adenocarcinoma, and fibrosarcoma, as well as osteosarcoma of the skull, may involve the facial nerve or one of its branches. Neurofibromas involving the vestibulocochlear nerve are very rare. Cranial nerves may be attenuated by compression from meningiomas lying on the calvarial floor. The vagosympathetic trunk can be compressed by aortic body tumors.

### **Diagnosis of Tumors of the Nervous System**

Diagnosis of a tumor of the nervous system is usually made using diagnostic aids which include plain-film radiography, contrast radiography (e.g., myelography), or specialized radiographic techniques, such as radionuclide imaging (scintigraphy), computerized tomography (CT), and magnetic resonance imaging (MRI). Plain-film radiography will detect evidence of bone neoplasia. Various references have been made to the use of specialized imaging, such as CT and MRI, for evaluating brain tumors (see individual tumors above). These techniques can provide important diagnostic information regarding axial origin, (e.g., extra-axial tumors: meningiomas, pituitary tumors, and intracranially invading nasal tumors; versus intra-axial tumors: including the various glial tumors, ependymoma, choroid plexus papilloma, medulloblastoma, etc.), anatomic location, shape, pattern of growth, signal intensity, edema, and enhancement characteristics of various brain tumors [7,29,117]. These criteria can be important factors in determining prognosis, outcome and therapy. MRI is considered the better method for detecting and characterizing intracranial tumors because of its superior depiction of soft tissues and relative lack of degrading artifacts [118]. While definitive diagnosis of intracranial tumors requires histopathological tissue biopsy evaluation, some indices of malignancy have been defined using MRI scans, for example, presence of edema, poor margin definition, invasion of tissues, and extension of growth across the midline [29]. Smear preparations of intracranial lesions, obtained either by computed tomography-guided stereobiopsy or from a craniotomy provide rapid and accurate intraoperative diagnosis of many primary nervous system tumors [199].

The following is a review of the myelographic characteristics associated with extradural, intradural-extramedullary, and intramedullary locations [85]: extradural lesions are located outside the dura mater and result in attenuation of the dural tube and spinal cord. Confirmation of an extradural lesion is made when the dye column is deflected away from the vertebral canal resulting in a widened epidural space. Intradural-extramedullary lesions are located in the subarachnoid space. A mass in this location acts as a wedge displacing the dura mater to the bony vertebral canal and the spinal cord to the contralateral vertebral canal. A characteristic cup or golf tee appearance is seen as the contrast material abuts the cranial and caudal margins of the tumor. In contrast, intramedullary tumors displace spinal cord substance from within, resulting in a circumferential enlargement of the spinal cord and accompanying attenuation of contrast material in the subarachnoid space around the tumor.

An evaluation of radiographic, myelographic and CT images has been reported in 16 dogs with histologically diagnosed vertebral or spinal cord neoplasia [119]. Radiographs were compared with CT images to evaluate vertebral bone changes (bone production, lysis or both), and myelographic and CT images were evaluated to classify lesions into extradural, intradural-extramedullary or intramedullary sites. Histologically, 7 lesions were vertebral tumors and were classified as extradural lesions; 10 lesions were spinal cord tumors of which 8 were classified as intradural-extramedullary and 2 as intramedullary. This study suggested that when evaluating extradural lesions, the amount of bone change was better visualized using CT than survey radiographs, and that myelography was better than CT for classifying spinal cord lesions. In another imaging study, twenty-one dogs with confirmed tumors of the spinal cord or paraspinal tissues were evaluated with MRI scans [94]. Bone infiltration was correctly assessed in all but one dog, and the anatomical locations (especially using sagittal T2-weighted images) were accurately determined in all dogs; however, localization of tumors in the intradural-extramedullary compartment was not always possible (in 3 of 9 dogs, the tumors were thought to be intramedullary). Transverse T1-weighted images pre and post Gd-DTPA administration were considered helpful for additional localization and definition of tumor extension. The marked, uniform contrast enhancement helped distinguish the intradural component of MPNSTs from the spinal cord. Myelographic interpretation of intramedullary spinal cord metastasis may be difficult and intramedullary tumors must be differentiated from spinal cord edema or hemorrhage [14]. Classically, with intramedullary masses, there is widening of the spinal cord shadow and tapering and attenuation of the contrast columns in both lateral and ventrodorsal views. Diagnosis of peripheral nerve tumors can be facilitated using electrodiagnostic techniques (electromyography, nerve conduction velocity determinations) in conjunction with myelography and imaging techniques, including CT, MRI, and ultrasonography. Myelographic studies are reportedly often negative with cervical MPNSTs [88], in which case, exploration of the brachial plexus can be useful to examine the color, size and texture of the nerve trunks, in conjunction with fascicular or nerve trunk biopsy. In a report of MPNST in 10 dogs involving the trigeminal nerve [112], CT imaging revealed an enlarged foramen and distorted rostral petrous temporal bone in one case, while MRI scans identified the lesion accurately in seven cases. Ultrasonographically and CT studies were used to define and facilitate percutaneous biopsy of a lumbosacral plexus nerve sheath tumor in a 10 year old dog [194].

Analysis of CSF from 77 dogs with primary brain tumors (including astrocytomas, choroid plexus papillomas, ependymomas, meningiomas, and oligodendrogliomas), revealed a moderately increased total protein content (e.g., 30 to 70 mg/dl), a moderate increase in total white cell count (usually mononuclear pleocytosis and typically < 50 cells/ $\mu$ l), and an elevated CSF pressure (e.g., from 180 to 250 mm of CSF) [33]. In this study, the CSF associated with meningiomas was unique in having a WBC count greater than 50 cells/ $\mu$ l and a WBC differential count greater than 50% polymorphonuclear (PMN) cells, which correlated with necrosis or PMN cell infiltration of the tumors. CSF protein was highest in dogs with choroid plexus papilloma (e.g., approximately 150 mg/dl) and CSF pressure was highest in dogs with ependymomas and choroid plexus papillomas (e.g., approximately 250 mm of CSF). While this and other studies [90] point to the low frequency of tumor cells in CSF from animals with brain or spinal cord neoplasia, malignant cells have been reported in dogs and cats with intracranial and spinal cord (extradural and intramedullary) lymphosarcomas [14,15,79,89] and in cats with oligodendrogliomas [195]. An intense mixed pleocytosis with numerous epithelial-like round, neoplastic cells were noted in a dog with meningeal carcinomatosis [18]. A CSF study of spinal lymphosarcoma in 23 cats revealed a nonspecific mixed pleocytosis (mean of 140 cells/ $\mu$ l) with elevated protein content (mean of 140 mg/dl). Interestingly, several cats had an increased neutrophilic population in association with hemorrhage and necrosis of the infiltrating tumor and adjacent spinal cord. An increase in CSF protein has been found in animals with intravascular lymphoma (malignant angioendotheliomatosis).

### **Prognosis and Treatment**

In general, prognosis of animals with tumors of the nervous system is guarded to poor, but will depend on tumor location, surgical accessibility, rate of tumor growth, and degree of damage to the nervous tissue. Based on more accurate localization and identification of brain tumors using sophisticated imaging techniques, such as CT and MRI, management of brain tumors has tended to evolve around surgical resection, radiation therapy, and chemotherapy. Identification and characterization of tumors from tissue biopsies using stereotactic-guided biopsy devices should prove to be very beneficial in establishing therapeutic modalities [120,121,199], since at present, many dogs with brain tumors are irradiated without histopathological diagnosis or cytoreductive surgery prior to irradiation [122]. While actual success rates for tumor types and locations are lacking at this time, it has been stated that cerebral tumors (including meningiomas and ependymomas) without brainstem signs carry the best prognosis, especially for cats [123,139], and several studies have shown that radiation therapy appears to be the most successful treatment for a variety of intracranial tumors [122,124-126,191], and if surgery is performed, postoperative radiation therapy appears to prolong survival times in dogs with brain masses. Radiation therapy is useful for inoperable tumors, and may be preferable to surgical resection in dogs if the mass appears infiltrative [122]. In a retrospective study of 86 dogs with brain tumors, in which definitive treatment included surgery, cobalt-60 radiation, whole-

body hyperthermia, <sup>125</sup>I implants, and chemotherapy, alone or in combination, dogs treated with cobalt-60 radiation, with or without other combinations of therapy, lived significantly longer than dogs who received surgery (+/- <sup>125</sup>I implants), or dogs that received symptomatic treatment [20]. Dogs who had a solitary site of involvement had a better prognosis. Also, dogs with mild-to-moderate neurologic signs had a more favorable prognosis compared with dogs that had severe initial neurologic impairment. Median survival times of dogs receiving no therapy or only symptomatic therapy, surgery (+/- <sup>125</sup>I), or cobalt-60 radiation (+/- hyperthermia, +/- surgery) were 0.2, 0.9, and 4.9 months, respectively. In this same study, dogs with normal CSF or with albuminocytologic dissociation had significantly longer survival time than dogs with an increased WBC count in the CSF. Long-term control of brain tumors using cytotoxic chemotherapy alone is poor [126,127], and symptomatic medical therapy, such as use of antiinflammatory doses of corticosteroids and/or anticonvulsants, is palliative at best. Corticosteroids may ameliorate signs by reducing edema around the tumor and may produce temporary regression of lymphoid and reticulohistiocytic tumors. Surgery is considered the primary therapeutic modality for meningioma in dogs [126,128,129]. In a report of meningiomas in dogs and cats treated by surgery alone, mean survival times were 198 and 485 days, respectively, with 1 year survival rates of 30% for dogs and 50% for cats [129]. Longer survival times can be anticipated with addition of irradiation [28,130] and/or cytotoxic drugs. Surgical fenestration and hematoma removal were effective in treating intracranial intra-arachnoid cysts and intracystic hemorrhage in 2 adult dogs, although the cyst persisted in 1 dog [203]. Gene therapy may become an important future treatment modality [131]. Endocrine therapy may have a role in the treatment of unresectable or recurrent meningiomas in dogs and cats [176].

Most extradural spinal tumors are either primary bone tumors (removal of which often results in decreased spinal stability, subluxation, or pathological fractures) or metastatic tumors, with possible sites elsewhere. Post-surgical survival times were low in one study of malignant extradural tumors in dogs (including osteosarcoma, plasma cell tumor, and metastatic endocrine cell tumor) [98]. A recent study of vertebral tumors (primary or metastatic osteosarcoma or fibrosarcoma) in 20 dogs supports the overall guarded prognosis for dogs with vertebral neoplasia [132]. These dogs were treated with combinations of surgery, radiation, and chemotherapy. All dogs died due to their disease, 15 died due to local failure, and five died due to nonvertebral metastasis. Overall median survival time was 135 days, with a range of 15 to 600 days. Postoperative neurological status was the only factor that had a significant influence on outcome. It was stated that better combinations of surgery, chemotherapy, and radiation therapy remain to be defined for these tumors. Note that tumor induction can be a rare late effect of radiation therapy of spinal tumors. In one report, lumbar vertebral osteosarcoma was identified more than 5 years following cytoreductive surgery and Cobalt 60 teletherapy in a Rottweiler diagnosed with an intradural extramedullary spinal cord tumor [207]. Modalities recommended for treating cats with spinal lymphosarcoma include surgical cytoreduction, focal radiotherapy (see radiation therapy), and systemic chemotherapy, including L-asparaginase, vincristine, and prednisone [89]. Long-term results were poor. In another study of spinal lymphoma in 21 cats [96], the majority of those necropsied having multicentric lymphoma, 9 cats were treated with chemotherapy alone. The complete remission rate was 50% in 6 cats given cyclophosphamide, vincristine, and prednisone. The median duration of complete remission was 14 weeks. Complete remissions were not observed in 3 cats given only corticosteroids. A single cat treated by laminectomy and postoperative chemotherapy had a prolonged remission (62 weeks). In another study, survival times for dogs with spinal lymphomas and myxomas-myxosarcomas ranged from 560 to 1080 days after surgical excision, although some dogs received post-surgical radiotherapy and chemotherapy [98]. An extradural ganglioneuroma was successfully treated with laminectomy and surgical resection, although tumor recurrence occurred after 12 months [93].

While a number of intradural-extramedullary tumors (e.g., meningiomas and lipomas) may be successfully removed at surgery and with long post-surgery survival [98], prognosis for animals with MPNSTs is generally poor since only a small percentage of the tumors in this location are completely resectable and their rate of recurrence is high [87,88,101]. Another complication is metastasis, often to the lungs. Intradural-extramedullary tumors that involve spinal cord segments of an intumescence or are ventrally located or invade adjacent neural parenchyma also have a poor prognosis [100]. Early diagnosis of MPNSTs may result in a greater degree of success. Mean survival of 180 days was reported in one study following MPNST surgical resection [98].

Intramedullary masses are generally not surgically resectable. However, successful removal of a thoracolumbar intramedullary ependymoma, and a tumor with characteristics of a nephroblastoma, by exploratory laminectomy followed by durotomy and myelotomy, has been reported [133]. Excision also resulted in a favorable outcome in a 9 year old dog with an intramedullary spinal cord hamartoma [201]. Prognosis for dogs with intramedullary spinal cord metastasis (most frequently associated with hemangiosarcoma and lymphosarcoma) is poor due to the frequent presence of disseminated disease, although temporary response to corticosteroid therapy may be achieved [14].

Peripheral nerve and nerve root tumors can be resected successfully [85,134,200], but it is sometimes necessary to remove the affected nerve and nerve root. Resection, with anastomosis of the nerve, is possible if the tumor is not too large. Recurrences are common following resection of peripherally-located tumors, and in one report, the average time to recurrence was 5 months [88]. Complete amputation of the limb may be required if more than one root is involved, as is

commonly found, or if atrophy of all muscle groups is extreme (as may occur with a tumor involving multiple nerves of the brachial plexus) [87,88,101]. In one report of dogs with MPNST involving the trigeminal nerve, surgery was performed for biopsy and lesion removal in three cases [112]. Cases not treated had a progressive course eventually resulting in euthanasia or death (with survival times ranging from five to 21 months). Of the cases treated surgically, one case had no disease progression 27 months after surgery.

### **Skeletal Muscle Tumors**

Skeletal muscle tumors are infrequently reported in dogs or cats. Those involving the limbs may result in focal swellings and lameness. Primary tumors such as rhabdomyomas or rhabdomyosarcomas appear to be rarely seen [190,206], while primary skeletal muscle lymphomas and vascular hamartomas are reported only sporadically [140,141]. Skeletal muscle rhabdomyosarcomas can be highly malignant tumors with a propensity for aggressive local invasiveness and metastasis and carry a very guarded prognosis [207]. Microscopic findings include non-cohesive, round/oval cells with hyperchromatic nuclei and strongly eosinophilic cytoplasm, and considerable mitotic activity. Interestingly, the majority of these tumors occur in tissues other than skeletal muscle. An invasive intracranial juvenile parameningeal rhabdomyosarcoma was reported in a 23 month old dog causing unilateral denervation atrophy of masticatory muscles [189]. There have been several reports of tumors metastasizing to skeletal muscles in dogs and cats, including malignant histiocytosis, epithelioid T-cell lymphosarcoma, and acute myelomonocytic leukemia [142-145]. In my experience, metastatic lymphosarcoma in canine skeletal muscle is relatively common. In some instances, there may be spread of tumors into muscle from surrounding tissues, such as periosteal sarcomas [146]. Imaging techniques (e.g., sonography) may suggest a diagnosis of skeletal muscle neoplasia [147], and confirmation may be made using cytopathology from surgical biopsy. Focal masses may be surgically resected and removed. Prognosis is guarded, even with chemotherapy and/or radiation therapy.

### **Paraneoplastic Disorders**

Paraneoplastic syndromes of the nervous system represent nonmetastatic complications of cancer. These "remote" effects are unrelated to metabolic or nutritional disorders, infection, stroke, or complications of therapy (e.g., chemotherapy), and are believed to be immunologically mediated [148-150]. The syndromes appear to be the result of molecular mimicry in which an immune response against a tumor antigen cross-reacts with a similar antigen expressed by neural tissues (usually neurons), although the exact pathogenesis remains unclear [151]. Several of these syndromes are characterized by presence of tumor-specific autoantibodies (termed anti-Yo, Hu, Ri) in CSF and serum [151] (the autoantibodies, which are predominantly IgG, are believed to be produced in the CNS [149]). For example, high titers of anti-Hu antibody occur in patients with paraneoplastic encephalomyelitis and subacute sensory neuropathy (in association with small cell lung cancers, neuroblastomas, and medulloblastomas); anti-Yo antibodies occur in patients with paraneoplastic cerebellar degeneration (in association with ovarian cancer, breast cancer, small cell lung cancer, and Hodgkin's disease); and anti-Ri antibodies are seen in patients with paraneoplastic opsoclonus-myoclonus (in association with neuroblastoma, and cancers of breast, gynecologic, or small cell lung origin). In people, these syndromes may precede tumor diagnosis by weeks, months, or even years and many are good diagnostic and prognostic indicators. Paraneoplastic syndromes affecting the nervous system in people include those involving the brain and cranial nerves, the spinal cord and dorsal root ganglia, the peripheral nerves, and the neuromuscular junction and muscle. While paraneoplastic disorders have become increasingly common in people with malignancies as therapy becomes more effective and the patients live longer [153], their overall incidence remains low, ranging from 1 to 7% of cancer patients [154,155]. However, the incidence varies with tumor type, e.g., it may be 4 to 5% in patients with breast cancer and up to 16% of patients with small cell lung cancer [156]. CNS paraneoplastic syndromes recognized in people are rarely documented in animals with malignancies, although the veterinary literature probably does not reflect the real incidence of this paraneoplastic disorder. A paraneoplastic syndrome involving the spinal cord has been described in an 8 year old, male German Shepherd dog [157]. The dog had a history of acute pelvic limb paralysis. Over a 10-day period, there was progressive loss of motor function, conscious proprioceptive deficits, and loss of superficial and deep pain sensation over the trunk and pelvic limbs. Schiff-Sherrington-like hyperextension developed as a late sign in the thoracic limbs. Necropsy revealed a hepatocellular carcinoma with metastasis to the lungs, liver, spleen, and lymph nodes. A severe necrotizing myelopathy was present throughout the thoracic spinal cord affecting gray and white matter - changes included spongy degeneration, gliosis, demyelination, axonal swelling and degeneration, and neuronal necrosis. In another report, a spectrum of neurological abnormalities in a 17 month old male Poodle was attributed to hyperviscosity syndrome secondary to macroglobulinemia-associated lymphocytic leukemia [158]. Paraneoplastic disorders of the neuromuscular junction in people are most commonly associated with Lambert-Eaton myasthenic syndrome (LEMS) in which autoantibodies act against neuronal voltage-gated calcium channels and subsequent decrease in acetylcholine release at neuromuscular junctions and autonomic nerve synapses [159]. Approximately 60% of patients with LEMS have small cell lung cancer [155]. To my knowledge, LEMS has not been reported in dogs or cats. Paraneoplastic myasthenia gravis (MG),

a postsynaptic neuromuscular disorder caused by antibodies against the nicotinic acetylcholine receptor is found in approximately 50% of human patients with thymomas [160-162]. Patients with thymoma-associated MG may also produce autoantibodies to a variety of neuromuscular antigens, including the muscle protein titin, skeletal muscle calcium release channel (ryanodine receptor, RyR), and voltage-gated potassium channels [162]. Acquired MG also occurs in dogs with thymoma. In one review, the average age of animals with thymoma was 8.7 years, German shepherd dogs accounted for 28% of the cases, and there was no sex predominance [163]. Approximately 47% of these dogs had MG, 33% had non-thymic cancer (including mammary adenocarcinoma, pheochromocytoma, and pulmonary adenocarcinoma), and 20% had signs of a polymyositis. Recently, titin and RyR antibodies were identified in dogs with MG and thymoma [164]. With respect to paraneoplastic syndromes and muscle, the association between myositis (e.g., dermatomyositis and polymyositis) and malignant neoplasms has been well established in people, and the reported clinical frequency ranges from 7 to 30% [165,166]. Some forms of myositis, such as dermatomyositis, can be especially significant markers of occult malignancy in people, including ovarian and breast cancer in women, and lung and gastrointestinal cancer in men [155]. A paraneoplastic necrotizing myopathy, with little inflammation, may occur in humans in association with a variety of tumors, including gastrointestinal adenocarcinoma, transitional cell carcinoma, prostatic carcinoma, and non-small cell lung carcinoma [167]. Weight loss and muscle weakness may be other independent prognostic factors in human patients with underlying malignancies, with more than 50% of human cancer patients suffering from cachexia [168]. Cytokines, produced by tumors or by the immune system, may mediate this cachectic process [169]. While necrosis and low-grade myositis is seen sporadically in dogs with malignant tumors, such as bronchogenic carcinoma, myeloid leukemia, and tonsillar carcinoma [170,171], the frequency of this suspected paraneoplastic association is presently unknown. Dogs and cats with histopathologically confirmed myositis/necrotizing myopathy who fail to respond to therapy, or who relapse, may merit similar malignancy evaluation as accorded people, including chest radiography, sonography, computed tomography and magnetic resonance imaging. This vigilance may detect tumors at a more treatable stage. Paraneoplastic changes also occur in peripheral nerves of people and are believed to occur in nerves of animals (paraneoplastic neuropathy).

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## Inflammatory Diseases of the Central Nervous System (6-Feb-2003)

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Inflammatory diseases form an important core of diseases of the Central Nervous System. By definition, neurological diseases of dogs and cats are characterized by central nervous system (CNS) inflammation. The one exception is feline spongiform encephalopathy, caused by an atypical infectious agent, a scrapie-like, transmissible prion protein. The hallmark of CNS inflammation is infiltration of peripheral blood leukocytes into the neuroparenchyma and its coverings, resulting in various types of encephalitis and/or meningitis, and sometimes associated with altered vascular integrity that leads to edema [1]. Miscellaneous inflammatory disorders such as diskospondylitis and otitis media-interna (both typically bacterial in nature) are discussed under Degenerative and Compressive Structural Disorders, and Peripheral Nerve Disorders, respectively.

The inflammatory diseases of the CNS have been divided into the following categories:

### Algal Disorders

Protothecosis

### Bacterial Disorders

Abscessation

Bacterial Meningitis

### Idiopathic Inflammatory Disorders

Eosinophilic Meningoencephalitis

Feline Polioencephalomyelitis

Granulomatous Meningoencephalomyelitis

Meningitis

- Steroid Responsive Meningitis-arteritis

- Miscellaneous meningitis/meningoencephalitis

Meningoencephalitis in Greyhounds

Necrotizing Encephalitis

- Pug Dog Encephalitis

Pyogranulomatous Meningoencephalomyelitis

Shaker Dog Disease

### Mycotic Diseases of the CNS

### Parasitic Encephalomyelitis

### Prion Protein

Feline Spongiform Encephalopathy

### Protozoal Encephalitis-encephalomyelitis

Toxoplasmosis

Neosporosis

Sarcocystosis

Encephalitozoonosis

Trypanosomiasis

Acanthamebiasis

Babesiosis

Leishmaniasis

### Rickettsial Disorders

Rocky Mountain Spotted Fever

Canine Ehrlichiosis

Salmon Poisoning

### Viral Disorders

Aujeszky's Disease

Borna Disease

Canine Herpes Virus Encephalomyelitis

Canine Distemper Encephalomyelitis

- Canine Distemper Encephalomyelitis in Immature Animals

- Multifocal Distemper Encephalomyelitis in Mature Animals

- Old Dog Encephalitis

- Chronic Relapsing Encephalomyelitis

- Post-vaccinal Canine Distemper Encephalitis

Feline Immunodeficiency Virus

Feline Infectious Peritonitis

Feline Leukemia Virus

Infectious Canine Hepatitis

La Crosse Virus Encephalitis

Parvovirus Encephalitis

Rabies

- Post-vaccinal Rabies

Tick-borne Encephalitis in Dogs

### Abscessation of the Central Nervous System

Infection of the CNS may result in an abscess (a circumscribed collection of purulent material within the CNS, its surrounding membranes, or in the epidural space) and/or much less frequently, collection of pus (empyema) in subdural or epidural locations [284]. The term "pyocephalus" refers to a purulent effusion within the cranium and is synonymous with "pyencephalus". In animals, the empyema tends to be in cranial subdural sites and in spinal epidural locations [8,549-551]. Abscesses within the CNS are uncommon in dogs and cats but may arise as a result of either metastasis from distant foci of infection (e.g., lung abscesses and bacterial endocarditis), by direct extension from sinuses, ears, and eyes, as a result of trauma (e.g., bite wound), or from contaminated surgical instruments (e.g., spinal needle) [1-11]. Brain abscess may also result from penetration of the cranial cavity and brain substances by an exopharyngeal foreign



body (e.g., sewing needle). Several instances of spinal epidural infection in the cat have followed tail fracture or a purulent granulomatous dermatitis involving the tail [5,12]. The common sites for direct extension are the cribriform plate and the inner ear, resulting in abscess formation in the frontal lobe and the cerebellopontine angle, respectively (see otitis-media-interna). Spinal epidural infections may also result from vertebral osteomyelitis or paraspinal abscess. Abscesses of hematogenous origin, such as those that spread from pulmonary infection, bacterial endocarditis, or congenital heart disease with right to left shunting, appear to have a predilection for the CNS parenchyma, especially in the hypothalamus and cerebral cortex, and particularly in less vascularized areas such as white matter and junctions of gray and white matter [1]. It is thought that neuraxial abscessation occurs preferentially in areas of focal ischemia or necrosis [13]. CNS abscesses are usually associated with bacteria, but are occasionally caused by fungi [9]. Aerobic bacteria such as *Streptococcus*, *Staphylococcus*, *Pasteurella*, and *Nocardia* may be more common than anaerobic bacteria as causes of CNS infection in dogs and cats [14]. Nevertheless, anaerobic bacteria such as *Bacteroides*, *Fusobacterium*, *Peptostreptococcus*, *Actinomyces*, and *Eubacterium* are reported to be important pathogens in animals that can cause either brain abscesses or subdural empyema [5,8,15]. *Actinomyces* typically spreads by direct extension, although brain and possibly vertebral abscesses may result from hematogenous dissemination [15]. A rare granulomatous/pyogranulomatous mass lesion caused by *Mycobacterium avium*, an aerobic tuberculous bacterium, was reported in a 4 year old Domestic Shorthair cat [580].

The neuropathological progression of brain abscess (alpha-*Streptococcus*) formation has been studied experimentally at sequential stages in dogs, and the findings correlated with the appearance on CT brain scans [16]. The evolution of brain-abscess formation was divided into four stages based on histological criteria: early cerebritis (days 1 to 3); late cerebritis (days 4 to 9); early capsule formation (days 10 to 13); and late capsule formation (days 14 and later). The cerebritis stage was characterized by prominent perivascular cuffing by inflammatory cells (e.g., neutrophils, macrophages and lymphocytes) in the area adjacent to the developing necrotic center. However, the early elements of capsule formation appeared with the presence of fibroblasts by day 5. The CT scans showed ring-shaped contrast enhancement by day 3. Delayed scans at 30 minutes revealed diffusion of the contrast material into the developing necrotic center, forming a solid lesion. In lesions that were well encapsulated (14 days and older), five distinct histological zones were apparent:

1. a well formed necrotic center;
2. a peripheral zone of inflammatory cells, macrophages, and fibroblasts;
3. the dense collagenous capsule;
4. a layer of neovascularity associated with continuing cerebritis; and
5. reactive astrocytes, gliosis, and cerebral edema (vasogenic) external to the capsule.

The CT appearance of well encapsulated abscesses showed a typical ring-shaped contrast-enhancing lesion. The diameter of the ring correlated best with the presence of cerebritis (perivascular infiltrates in the adventitial sheaths of vessels surrounding the abscess). Brain abscesses can be an important complication in immunosuppressed patients. Experimental studies in immunosuppressed dogs suggested an initial reduction in mass effect from the brain abscess due to decreased inflammatory response and edema formation but that the eventual size and area of the abscess became larger than in controls due to the less effective host response and to delayed collagen formation and capsulation [17]. It should be noted that more virulent organism such as *Staphylococcus aureus* can produce larger CNS abscesses, earlier ependymitis, delayed progress toward healing, greater white matter destruction, and cause areas of inflammatory escape outside the collagen capsule [18]. In spontaneous CNS abscesses, organisms are often found in chains or small colonies, often within leukocytes [1]. A diffuse leptomeningitis may accompany a brain or spinal cord abscess. In addition, CNS embolization may occur during an acute septicemic infection [1].

Brain abscesses are life threatening due to systemic and local toxicity (in early stages of cerebritis) and increased intracranial pressure (during/after capsule formation) [19]. Capsules may rupture into the ventricle or subarachnoid space resulting in the formation of multiple abscesses [20]. Capsule formation may be rudimentary unless the abscess is close to the meningeal surface [1]. When abscesses are multiple, death occurs after a short clinical course. Prolonged survival may occur when abscesses are isolated; however, with brainstem abscesses, the clinical course is usually short because of interference with vital centers. Clinical signs will usually reflect a focal syndrome (e.g., cerebral, pontomedullary, or spinal cord syndrome) suggesting a space occupying lesion, or a multifocal syndrome associated with many small microabscesses. External fistulae have been observed in animals with vertebral actinomycosis [15]. Dogs with spinal epidural abscess/ empyema may present with fever, anorexia, lethargy, apparent spinal pain and paraparesis/paraplegia [549-551]. Spinal cord changes in animals with spinal epidural empyema may include focal areas of ischemic neuronal necrosis, intraparenchymal hemorrhage, and fibrinopurulent meningomyelitis [551].

Antemortem diagnosis is difficult. Leukocytosis, with or without left shift, and hyperglobulinemia may be found in blood analysis [15]. Fever is an inconsistent finding. Imaging techniques, such as CT and MRI scans, may facilitate early detection of CNS abscesses [21-23,564]. It should be noted that when an abscess becomes encapsulated there might be no evidence of infection and no systemic reaction. Accordingly, CSF evaluation may be of little value in excluding an

abscess from the differential diagnosis. Indeed, CSF collection may be contraindicated because of the risk of brain herniation. It has been suggested that CSF should only be collected after a CT or MRI has ruled out the presence of a mass lesion or after reducing intracranial pressure using such techniques as hyperventilation, administration of mannitol, etc [8]. In some animals in which CSF has been collected, marked increase in both leukocyte numbers (especially neutrophils) and protein has been found [8,9,564], and raised intracranial pressure is to be anticipated. Abnormal CSF analysis may also suggest rupture of a brain abscess into the ventricular system [564]. CSF analysis may be normal in animals with intraspinal abscessation [24], although a neutrophilic pleocytosis along with peripheral neutrophilia and variable concurrent diskospondylitis have been reported in dogs with spinal epidural empyema [549-550]. In a dog with a subvertebral mass, associated with actinomyces, that spread to compress the spinal cord, radiography revealed productive and destructive bony changes on the ventral surfaces of the first three thoracic vertebrae and adjacent ribs [15]. Myelography usually reveals focal/multifocal extradural spinal cord compression in animals with spinal epidural abscess/empyema, while CT scans show a mass effect with hypodense area within the vertebral canal [550,551].

Treatment of abscesses centers around antibiotic therapy, often for long periods, based on culture and drug sensitivity testing of organisms isolated from the abscess. When cultures cannot be obtained, a broad-spectrum antibiotic, such as penicillin (e.g., ampicillin at 5 - 22 mg/kg, IV, qid) in conjunction with chloramphenicol (at 10 - 15 mg/kg, PO, qid) or metronidazole (10 - 15 mg/kg, PO, tid), should be used [8,25,26]. Prognosis is guarded, especially if the mass lesion is large and encapsulated which may make it refractory to antibiotic therapy. Surgical decompression by craniotomy, burr holes, or laminectomy/surgical decompression may be indicated in cases of cranial subdural or spinal epidural/empyema [8,12,549-551]. Recent studies suggest that surgical decompression and long-term antibiotics may result in a favorable prognosis in dogs with spinal epidural empyema [549,550].

### **Aujeszky's Disease**

This disease, also known as pseudorabies, mad itch, and infectious bulbar paralysis, affects most species of wild and domestic animals except horses. Swine are the natural host of this virus (*Herpesvirus suis*/porcine herpesvirus I), and adult pigs (domestic and feral) may serve as inapparent carriers of infection and shed virus. Aujeszky's disease in dogs and cats may be the first indication that the disease is present in swine on a farm. Aujeszky's disease in species other than swine, namely cattle, dogs, cats and wildlife, is usually fatal, seemingly associated with the enhanced virulence and neurotropism seen in nonporcine species [1]. The virus reaches the CNS by traveling centripetally (retrograde) in the peripheral nerves, probably in the axoplasm of motor and sensory nerves [27-29]. Experimentally, anterograde transport (slower than retrograde transport), transneuronal, and trans-synaptic transport have also been shown [29,30]. The mode of transmission to dogs and cats is usually via the consumption of virus-contaminated tissues of swine, cattle, rats, mice or raccoons. The virus may also gain entrance to the body via scratches or abrasions from contaminated objects. In cats, experimental studies suggest the tonsils are a portal of entry with the virus subsequently moving along the pathways of the sensory branches of the ninth and tenth cranial nerves, the tractus and nucleus solitarius and the area postrema in the medulla [28]. Dogs with Aujeszky's disease apparently do not shed sufficient virus to infect other dogs housed with them.

The incubation period in the dog and cat ranges from 2 to 10 days. Death usually occurs within 24 to 48 hours after onset of clinical signs [31]. Classically, the most characteristic clinical manifestations are intense localized pruritis of face or limbs, with scratching or chewing to the point of self-mutilation. However, pruritis may not always be a constant feature [31,32]. Early in the course of the disease, excessive salivation, fever, restlessness, anorexia, emesis, and dyspnea may be noted, followed by incoordination, vocalization, anisocoria, ptosis, trismus, cervical rigidity, and muscle spasms. In one report encompassing 25 confirmed cases of canine Aujeszky's disease, 36% of the dogs showed signs of aggression [31]. Convulsions, coma, and death quickly ensue. The course of the disease can be so rapid in dogs and cats that death may occur without any clinical signs [33].

The virus is highly neurotropic, especially for CNS gray matter, and the most extensive brain changes in the dog and cat occur in the medulla, followed by the pons, thalamus, cerebellum, and cerebral cortex. Microscopically, a moderate meningoencephalomyelitis and nonsuppurative ganglionitis is observed, with perivascular mononuclear infiltrations, proliferation of neuroglia, microabscessation, as well as Cowdry type A intranuclear inclusions in glial cells, ganglia and neurons [34]. Neuronal degeneration and neuronophagia have been reported in spinal and myenteric ganglia, spinal cord gray matter, medulla, and pons [35,36]. A ganglioneuritis of the stellate ganglia and autonomic ganglia within the heart has been noted in experimental dog studies, associated with fatal arrhythmias [37]. Karyorrhexis of the inflammatory cells and microglia is commonly found in dogs and cats [1].

Diagnosis may be suggested by clinical and neuropathological findings and confirmed by fluorescent antibody test of brain tissue, by laboratory animal (usually rabbit) inoculation with tissue extracts, or by virus isolation in cell culture. In addition, immunohistochemistry and *in situ* hybridization techniques are now available to confirm presence of Aujeszky's disease virus infection in paraffin-embedded tissues [38]. Eliminating consumption of infected tissues can

prevent the disease. All offal fed to dogs should be cooked. A safe, reliable, effective vaccine for dogs and cats remains to be marketed. Treatment does not alter the course of the disease.

### **Borna Disease**

Borna disease virus (BDV) can express neurotropism in a variety of species [568]. Borna disease has recently been described in several dogs (in Europe and Japan) with acute, progressive neurological signs associated with a nonsuppurative meningoencephalitis dominated by large perivascular cuffs consisting of lymphocytes, macrophages and plasma cells; also present were inflammatory cell infiltrates in the neural parenchyma, neuronophagia and focal gliosis [566,569]. Single or multiple eosinophilic intranuclear Joest-Degen inclusion bodies were found in neurons. Neuronal BDV antigen and BDV-specific RNA were demonstrated in the brain and spinal cord. An apparent intracerebral T-cell immune response has been reported in cats naturally infected with BDV [572]. A variety of clinical signs were reported including ataxia, personality change, staring gaze, and increased vocalization. Affected cats had a moderate/severe non-suppurative meningoencephalitis. A clinical variant of confirmed Borna disease in a cat was characterized by muscle fasciculations and proprioceptive deficits [581]. BDV may be the etiological agent associated with staggering disease in cats (see Feline Polioencephalomyelitis).

### **Canine Herpesvirus Encephalitis**

Fatal herpes virus encephalitis has been seen in young puppies [39-41]. Transmission occurs *in utero*, by direct contact with diseased littermates, or by inhalation or ingestion of infected material. The virus is believed to spread to the CNS via the hematogenous route, after initial replication in the oronasopharynx. However, ganglioneuritis of the trigeminal nerve is also reported to be a frequent lesion in puppies infected by oronasal exposure, and the virus may travel to the CNS via the peripheral nerve [42]. The high susceptibility of newborn puppies to disseminated canine herpesvirus (CHV) infection is related to their relatively low body temperature and immune status [43]. The infection is self-limiting beyond 3 weeks of age and puppies at 6 weeks of age are resistant to experimental infection [44]. Older puppies appear to be resistant to the virus and can serve as asymptomatic carriers of CHV. Experimental studies indicate that active infections, with viral shedding, may occur repeatedly for prolonged periods following immunosuppressive doses of prednisolone [45,46].

The syndrome is characterized by acute onset of signs including crying, diarrhea, dyspnea, and abdominal tenderness. Terminal depression and death usually occur 1 to 3 days after the onset of clinical signs. Diagnosis is based on age, clinical signs and pathological findings. At necropsy, ecchymoses and foci of necrosis are found in lung, liver, and kidney, along with diffuse pulmonary congestion, and splenomegaly [47]. In the CNS, acute encephalitis is a feature of this disease [40]. The main lesions are focal or laminar areas of necrosis involving mainly the Purkinje cell and granular layers of the cerebellum. Focal gliosis and perivascular cuffing by lymphocytes and macrophages are often seen in cerebrum, thalamus, and pons. Intranuclear inclusions may be observed occasionally in neurons and glial cells adjacent to the malacic areas. Meningitis, with necrosis of capillary walls, may be found. Perivascular edema and hemorrhages occur in many visceral organs. Puppies surviving acute disease may develop cerebellar dysplasia [48]. Polyneuritis and ganglioneuritis of craniospinal and sympathetic ganglia have been reported [41].

### **Canine Distemper Encephalomyelitis**

Canine distemper encephalomyelitis (CDE) is caused by a paramyxovirus (genus Morbillivirus) closely related to measles virus of man, to Rinderpest virus of cattle, and to pestes des petits ruminants virus of sheep and goats [1,49]. The suggested link between dogs with canine distemper virus (CDV) and multiple sclerosis in people [50] has not been substantiated [51-53]. Although the incidence is decreasing, CDE is still a common CNS disorder in the dog, primarily in unvaccinated dogs but also occasionally in those dogs with a vaccinal history [1]. Young dogs are especially susceptible to infection, although older dogs are also at risk. While there are several different strains of the virus, there is only one serotype which means that exposure to one strain protects dogs against any subsequent challenge [1]. The virus is most commonly spread by aerosol exposure, although rarely, the virus may be spread transplacentally [54]. Dogs that are not immunized regularly may lose their protection and become infected following stress, immunosuppression, or contact with diseased animals [55]. Fifty to 75% of susceptible dogs are subclinically infected but clear the virus from the body, probably through antiviral antibodies, natural killer cells, and antibody-dependent cell mediated cytotoxicity [1]. Factors predisposing to development of clinical disease are multifactorial, including age, vaccination status, breed, and viral virulence (e.g., Snyder Hill and R252 strains are highly virulent and neurotropic) [55]. In addition, the clinical course, severity of the disease, and neuropathology have been shown experimentally to vary with the virus strain [56]. While the different strains all produced an encephalomyelitis, infection with Snyder Hill strain of CDV was consistently acute; dogs either succumbed 14 to 19 days post-inoculation or recovered. Lesions in the neuraxis were those of a polioencephalomyelitis. In contrast, CDV strain A75 - 17 produced subacute to chronic disease in which demyelination was the predominant finding. Some dogs succumbed, generally around 28 to 42 days post-inoculation, while others recovered. Some dogs developed persistent CNS infection but remained clinically stable until electively euthanized, up to 62 days post-inoculation. CDV strain R252 also induced delayed, predominantly white matter disease with a mixed pattern of mortalities, persistent infections and recoveries, similar to A75 - 17. Neutralizing antibody responses

correlated with the disease course. Dogs which died had low serum titers or lacked serum antibody. Recovering dogs had the earliest and highest titers. A few dogs with persistent CNS infection had antibody in the cerebrospinal fluid also.

Virus replication initially begins in lymphoid tissues. The initial systemic phase of infection by this virus is marked by immunosuppression [57]. Virus reaches the CNS approximately 1 week after infection by virus-infected lymphocytes, monocytes, and platelets associated with immune complexes [58-60]. Spread of virus through cerebrospinal fluid pathways may explain the frequent distribution in subependymal areas throughout the CNS [61]. A rapid and high-titered viral antibody response to CDV is crucial for recovery from viral infection with minimal or no clinical signs. Dogs unable to mount an adequate response develop a rapidly progressive disease and die [62]. Dogs that mount a delayed or intermediate response tend to develop chronic neurological disease.

Lesions may be found in gray and white matter. The earliest changes seen in the CNS are degenerative and appear to be the result of viral replication in glial cells, especially astrocytes [63], followed by viral-induced demyelination [61], while a non-suppurative inflammatory component occurs later, perhaps as viral immunosuppression is declining, and becomes superimposed on the degenerative lesion, although both may be seen together [1,64]. The role of T cells, which have been found at lesion sites, in the development of acute demyelination remains uncertain [65]. It has been suggested that massive invasion of T cells in the brain requires CDV expression in the CNS [576]. Vandeveld and colleagues have reported that this early, acute demyelination in distemper is also associated with a restricted CDV infection of oligodendrocytes which down-regulates the expression of a variety of cellular genes, in particular those coding for myelin proteins [66,67]. The degree of myelin destruction has been correlated with the amount of viral antigen in the tissue [61]. Inflammation during the latter stages of the infection appeared to be associated with viral clearance from the CNS in most dogs [61] but may lead to further damage of the white matter [68]. Ultrastructural findings include evidence of segmental demyelination with stripping of compact myelin by macrophages, ballooned myelin sheaths that are split at the intraperiod line, and numerous naked axons [1,69]. Oligodendrocytes numbers decline in areas of white matter injury, partly due to restricted CDV infection, but significant numbers remain even in chronic demyelinating lesions [563], even though it has been reported that CDV has no obvious tropism for oligodendrocytes [70]. At this time, the mechanism(s) leading to alteration and depletion of oligodendrocytes remains unexplained [71]. Whether progressive demyelination in chronic disease is immune-mediated [72] or associated with some other mechanism, such as macrophage-mediated bystander demyelination [73], remains an area of active research. It has been reported that viral persistence in the CNS is associated with decreased expression of viral surface proteins [74]. Dogs with chronic disease produce systemic and intrathecal IgG, anti-CDV antibodies, and antimyelin antibodies, especially against myelin basic protein [1,75,76]. These systemic humoral and cellular responses show little correlation with the disease course, are not necessarily protective, and can be accompanied by persistent viral presence within the CNS [68,74,75,77]. Restricted virus infection in the gray matter might represent a mechanism for viral persistence in distemper polioencephalitis [78]. Disease initiation and progression in early distemper leukoencephalomyelitis might be due to increased expression of pro-inflammatory cytokines and lack of up-regulation of anti-inflammatory cytokines [575]. Experimentally, the presence of interferon in CSF is considered a valuable marker for persistent CNS infection [79].

Several clinical syndromes associated with distemper have been recognized in dogs [80-82,560]. These are discussed below.

**Canine Distemper Encephalomyelitis in Immature Dogs** - This is the most common form of distemper virus infection and is often initially characterized by systemic evidence of gastrointestinal and respiratory disturbances: vomiting, diarrhea, coughing, and seromucopurulent oculonasal discharges. Hyperkeratosis of the footpad may be seen. Additionally, many animals have conjunctivitis and chorioretinitis. However, in one clinical report, only one third of the canine distemper cases had extraneural involvement [83]. These systemic signs may precede, or occur simultaneously with, neurological signs. Neurological signs are quite varied, often asymmetrical, and usually suggest a multifocal distribution of lesions [77,83]. Cortical and subcortical signs include generalized seizures and sometimes personality changes, such as depression and disorientation. Signs of localization in the brain stem include incoordination, hypermetria, falling, head tilt, and nystagmus. Occasionally, monoplegia and paraplegia are observed. A sign that is characteristic of distemper encephalitis is myoclonus (generalized or localized), or more correctly, flexor spasm [84,560]. Appendicular flexor muscles, abdominal muscles, and the cervical musculature are most frequently involved. Sometimes the masseteric, temporalis, and periorbital muscles are affected. These rhythmic contractions are not necessarily associated with limb paresis or paralysis and usually persist during sleep. The movements are temporarily abolished by intravenous injection of local anesthetic agents. An abnormality in the motor neuron-interneuron pool in the spinal cord is thought to cause the muscle contractions. Contractions are not dependent on sensory nerves or descending pathways from the brain. Acute visual impairment (optic neuritis), typically accompanied by dilated, unresponsive pupils, may be the only clinical sign in some dogs. Canine distemper virus is a common cause of convulsions in dogs less than six months of age. Olfactory dysfunction has been reported in affected dogs [85,86]. Neonatal infection prior to eruption of permanent dentition can cause enamel hypoplasia. Cell-mediated immunosuppression can occur with CDV, predisposing

affected animals to other infectious agents, including *Toxoplasma gondii* and *Neospora caninum* [83,87]. Increased levels of antibodies to canine distemper virus have been found in serum and synovial fluid of dogs with rheumatoid arthritis [88,89].

Softening, brownish discoloration and sometimes hemorrhage may be found macroscopically in the CNS [1]. Microscopic lesions may be found in many of the visceral organs including the bladder, kidney, gastrointestinal tract, bronchioles, and tonsils. Lesions in the CNS may involve both white and gray matter. Summers and colleagues state that pure gray matter disease (polioencephalitis or polioencephalomyelitis) is rare but when observed usually occurs in young puppies [1]. Overall, pathological findings may be characterized by mononuclear perivascular cuffing, gliosis, microglial proliferation, and inflammatory cell infiltration of the pia-arachnoid membrane. Adventitial cell proliferation and endothelial swelling are commonly seen. Neuronal changes including nuclear pyknosis and shrunken cells, chromatolysis, and neuronophagia are found in the cerebral cortex, pontomedullary nuclei, Purkinje cells, and gray matter of the spinal cord. In some dogs, hippocampal cells can be selectively involved [90]. Intranuclear and intracytoplasmic inclusion bodies may be present in neuronal cells, astrocytes, histiocytes, meningeal cells, and ependymal cells. The distribution of inclusion bodies in distemper virus encephalitis is erratic and their presence is not an indication of the severity of the disease process. Changes in the white matter vary according to the duration and intensity of the infection. There is an apparent predilection for the central white matter of the cerebellum, the cerebellar peduncles, the optic nerves and tracts, rostral medullary velum, hippocampal fornix, and the spinal cord [1]. Demyelinating lesions can be focal or disseminated, isolated or confluent. Nerve fibers may undergo degeneration, resulting in the formation of swollen axonal ovoids. Pronounced gliosis may be evident in association with these changes. In many severe lesions, there is evidence of tissue necrosis, edema, and macrophage infiltration. These lesions are often situated in the cerebellar peduncles or central white matter. Dogs with persistent CNS infection and chronic distemper encephalomyelitis harbor virus persistently in the uvea [91]. Recent studies suggest that restricted virus infection in the gray matter might represent a mechanism for viral persistence in distemper polioencephalitis [78]. Note that the pathological findings are often mild making accurate clinicopathological correlations difficult or impossible [1,83]. The distemper virus has been incriminated as a cause of bilateral polioencephalomalacia in dogs [92-94], although the relationship of malacic lesions to seizure-induced hypoxia-ischemia remains a possibility.

**Multifocal Distemper Encephalomyelitis in Mature Dogs** - In mature dogs between the ages of 4 and 8 years, canine distemper virus can produce a type of multifocal encephalomyelitis (MDE) that is characterized by a chronic course [80,81]. It is not unusual for an animal to be presented with a history of neurological signs that have been present for 12 months or more. The incidence of this disease is relatively low and does not appear to be related to breed or sex. Animals that have received vaccinations against distemper virus may be affected. This disease is not preceded by, nor is it coincident with, the systemic signs that are seen in younger dogs. Furthermore, it is not unusual for this slowly progressive disease to remain clinically and pathologically static. The initial neurological signs that are commonly seen in mature dogs with MDE include weakness of the pelvic limbs, generalized incoordination, and occasional falling. These signs frequently progress to tetraplegia. Generalized seizures or personality changes are not features of this disease and affected animals maintain a normal mental state. Many dogs will have unilateral or bilateral menace deficits, with normal or abnormal pupillary reflexes. Some animals will have signs of facial paralysis, head tilt, and nystagmus. Although head tremors may be seen, myoclonic movements or flexor spasms are usually not observed. Fecal and urinary incontinence and priapism have been reported in a 4 year old dog with multifocal distemper encephalomyelitis [95]. The pathological findings that occur in mature dogs with MDE are usually restricted to the CNS. The lesions tend to be multifocal and necrotizing and are frequently found in the cerebellopontine angle adjacent to the fourth ventricle, in the cerebellar and cerebral peduncles, in the central cerebellar white matter, in the optic tracts, and in spinal cord white matter. Cystic lesions may be noted along with a loss of the original architecture of the tissues and strong fibrillary astrogliosis. The focal lesions may be associated with thick, perivascular, mononuclear cuffs. Small, plaque-like demyelinating lesions may be found in the capsula interna and corona radiata. Inclusion bodies are rarely found and, when present, are usually located within astrocytic nuclei. Lesions generally are not found in the cerebral cortex.

**Old Dog Encephalitis** - Old dog encephalitis (ODE), in which canine distemper virus has been incriminated as the etiologic agent, is a subacute or chronic progressive panencephalitis that occurs rarely in mature dogs. ODE is also known as disseminated encephalomyelitis in mature dogs, subacute diffuse sclerosing encephalitis, and chronic dementional distemper. Affected animals are usually over six years of age; however, younger dogs may be affected. There are no related systemic signs, nor is there any apparent predisposition according to breed or sex. There is some speculation that this form of distemper no longer exists since no spontaneous cases have been observed at several institutions over the past decade. The most common initial neurological sign is visual impairment. ODE is an invariably progressive disorder and is accompanied by the development of increasing mental depression, compulsive circling, hyperkinesia, and head-pressing against objects (obstinate progression) [96]. A bilateral menace deficit of a central or peripheral nature is also a common sign. An affected animal may manifest a personality change and fail to recognize its owners. Signs of involvement of the brainstem are rare. Pathological findings associated with the disorder are restricted

to the CNS and are characterized by disseminated perivascular infiltration with lymphocytes and plasma cells, diffuse microglial proliferation, astrogliosis, neuronal degeneration, and neuronophagia. The lesions have a diffuse distribution throughout all divisions of the cerebral cortex. Similar lesions are usually found throughout the basal nuclei, thalamus, hypothalamus, and midbrain. The perivascular mononuclear cuffs often extend beyond the Virchow-Robin space and infiltrate the nervous parenchyma. Diffuse demyelination is seen in subcortical areas, internal capsule, and cerebral peduncles, and often is observed in the pontine area and middle cerebellar peduncles. Large eosinophilic inclusion bodies are seen in the nuclei and cytoplasm of neuronal and glial cells. Necrotizing lesions may be present in the cerebral cortex, characterized by diffuse loss of neuronal cells with replacement by fibrillary astrocytes.

ODE is clinically and pathologically different from MDE in mature dogs. The nature of the lesions (diffuse sclerosis versus multifocal necrosis) and their topographic localization (cerebral cortex and upper brain stem versus lower brain stem and spinal cord) are quite distinct in ODE and MDE, respectively. In contrast to MDE, the cerebellum is mostly spared in ODE. Clinical differentiation between the two diseases is facilitated by the development of progressive cortical and subcortical signs (mental depression, unresponsiveness, obstinate progression) in old dog encephalitis. Also, experimental transmission of distemper encephalitis from young dogs and from dogs with MDE has been relatively easy [97], but is more difficult in dogs with ODE [98]. The interest generated by ODE is related to its clinical, pathological, and immunological similarities with subacute sclerosing panencephalitis in man [99,100] even though there appears to be different mechanisms operating in the maintenance of persistent infection and pathogenesis of these two chronic viral diseases [101]. Recently, experimental infection of a gnotobiotic Beagle dog with the neurovirulent R252 strain of CDV resulted in long-term CNS infection in which cerebral and brain stem lesions were consistent with ODE [102].

**Chronic Relapsing Encephalomyelitis** - There have been occasional reports of dogs with a chronic relapsing course [82,83]. In one case, an 18 month old mixed-breed male dog with spontaneous canine distemper virus infection associated with chronic progressive multiphasic neurological disease, initial neurological deficits in the pelvic limbs progressed rapidly to paraplegia with almost complete remission after 9 weeks [82]. This was followed by another acute episode with severe, progressive thoracic limb weakness, muscle atrophy and proprioceptive deficits, coarse head tremors, and neck myoclonus over the ensuing 3 months, along with rising serum neutralizing anti-CDV titers in the serum and CSF. Three distinct CNS lesions were identified: spinal cystic necrosis, chronic demyelination in the cerebellum, and acute demyelination in the pons. Persistent CDV antigen was demonstrated immunocytochemically only in acute lesions and was restricted to neurons. The immunological mechanism associated with the distinct remissions and exacerbations and CDV antigen clearance from chronic demyelinating lesions but persistence in acute lesions, despite a vigorous anti-CDV serologic response, was not defined.

The diagnosis of canine distemper encephalomyelitis (in young dogs, especially) is usually based on history and clinical signs. The index of suspicion is higher in affected dogs that have not been vaccinated. Positive diagnosis may be made through use of immunofluorescent or immunocytochemical techniques to detect canine distemper viral antigen in brain sections and other tissues (e.g., mononuclear cells in blood smears, conjunctival or tracheal washes, or footpad biopsies) [77,103-106]. In one study, immunostaining was prominent in early and subacute and reduced in chronic demyelinating lesions [106]. These techniques are considered superior to the demonstration of inclusion bodies or syncytial cells for the confirmation of CDE [107]. Ophthalmoscopic examinations may detect a chorioretinitis [108] characterized by areas of hyperreflectivity and bright colored "medallion" lesions, indicative of past or latent infection. Hematological and biochemical data are non-specific, although many affected dogs will be lymphopenic during the acute phase of illness [77,83], and electroencephalographic traces may indicate presence of inflammatory disease. CSF analysis may reveal a moderate pleocytosis (15 to 60 WBCs/ $\mu$ l) of mononuclear cells (lymphocytes and macrophages), and elevated gamma globulins [109], although during the acute demyelinating stage of the disease, inflammatory reactions may be limited or lacking and CSF protein/cell count may be normal [76]. Eosinophilic intracytoplasmic inclusion bodies have been reported in CSF mononuclear cells [110], although their detection is rare. Increased  $\beta$ -glucuronidase levels have been reported in serum and CSF [111]. Specific neutralizing antibody in CSF occurs 2 to 3 weeks after onset of disease and is the most definite evidence for canine distemper. It is normally not present in the CSF of vaccinated dogs, dogs that develop circulating antibody quickly and remain asymptomatic after exposure, or dogs that die from acute CDV infection [103]. A competitive enzyme-linked immunosorbent assay (cELISA) has been described as a screening test for suspect CDV in sera from dogs [112]. The IgG index (a calculated quotient using IgG and albumin contents of CSF and serum to detect intrathecal IgG synthesis) has been reported to be elevated in most dogs with distemper (with the exception of dogs with acute non-inflammatory distemper), even in cases in which no significant pleocytosis is found [83,113]. This index, however, is not specific for distemper [114]. Detection of CDV in urine using polymerase chain reaction (PCR) amplification has been recently reported as a useful routine screen for dogs with suspected distemper encephalomyelitis [529].

Prognosis is guarded. Seizures are an unfavorable prognostic sign [83]. Curiously, dogs with impetiginous dermatitis rarely develop CNS disease [55]. Dogs with low CSF IgG titers (< 1:100), low CSF cell counts, low gamma-globulin

levels, and high CSF albumin levels usually develop acute, fatal disease; whereas, dogs with high CSF IgG titers (> 1:100), high CSF cell counts, and sustained increase in gamma-globulin levels with normal or transient increase in albumin concentration may have a better prognosis for recovery [110,115,116]. Recent studies suggest that measurement of CD4 positive T cells in serum may have prognostic value in clinical cases: with recovery associated with normal or mild depletion but severe disease being associated with pronounced T-cell depletion [554].

There is no treatment for CDE, except supportive, and dogs with progressive neurological signs leading to incapacitation need to be euthanized. The prognosis is better in dogs with non-progressive neurological complications, such as intermittent seizures, myoclonus, and visual impairment, although only seizures may respond to medication.

**Post-vaccinal Canine Distemper Encephalitis** - Post-vaccinal canine distemper encephalitis occurs in young animals, especially those less than six months of age. It has been recognized as a disease entity for a number of years and is believed to be associated with vaccination using live virus [117-119]. The pathogenesis of this disease is unclear. It may result from:

- a. insufficient attenuation of the vaccine virus which causes subsequent infection of the CNS,
- b. the triggering of a latent distemper infection by vaccination,
- c. other vaccine components, or
- d. an enhanced susceptibility of the animal (e.g., animals that are immunosuppressed).

There is one report of post-vaccinal distemper in puppies immunosuppressed as a result of canine parvovirus infection [120]. Clinical signs are usually seen within one to two weeks after vaccination. They include anorexia, listlessness, and slight pyrexia. Neurological signs occur one to three days after the onset of these nonspecific signs. Sudden changes in temperament, viciousness (attacking owners, other animals, and inanimate objects), aimless wandering, howling, incoordination, and terminal convulsions may be seen in acute cases of approximately 24 hours' duration. In subacute cases (a disease course of 2 to 3 days), pelvic limb incoordination, circling, depression, and visual impairment are frequently observed. Clinical signs dominated by narcolepsy-cataplexy have also been reported in a 10 month old dog with presumed post-vaccinal distemper [121]. Cerebrospinal fluid analysis may reveal elevated protein levels and a mononuclear pleocytosis. Pathological findings in the brain are dominated by gray matter lesions including multifocal neuronal degeneration, neuronophagia, axonal degeneration, perivascular cuffing, and mild to moderate gliosis. The lesions are seen at all levels but tend to be most severe in the ventral pontine area, where malacia may also be present. Purkinje cells frequently remain unaffected. Intranuclear and intracytoplasmic inclusion bodies are present in many neuronal cells. Ultrastructural examination of the inclusion bodies reveals the presence of nucleocapsids having paramyxovirus features [118,119].

This disorder differs clinically from spontaneous distemper infection in young dogs by an altered personality (viciousness) that is very similar in nature and clinical course to that seen in the furious form of rabies encephalitis. Pathologically, post-vaccinal distemper encephalitis is distinguished from spontaneous distemper infection by the virtual absence of both visceral inclusions and demyelination in the area of cerebellopontine angle, the presence of many neuronal inclusions, diffuse pontine tegmental malacia, and large numbers of degenerating axonal ovoids. Prognosis is guarded and treatment is symptomatic.

There has been a report of the transmission of vaccinal virus to "in-contact" animals [122]. A 5 year old Labrador Retriever bitch, which had whelped 10 puppies three days previously, was given booster vaccination against distemper, adenovirus, parvovirus, parainfluenza virus and leptospirosis. Eighteen days later, neurological signs (including seizures, crying/screaming, twisting of head/neck) were noted in some puppies, five of which were euthanized. Pathological findings in brain were similar to those described above, and, together with serological findings, suggested that vaccinal rather than field distemper virus was the cause of the encephalitis. The vaccination of pregnant bitches with attenuated live distemper virus vaccines is not recommended and vaccination of recently whelped bitches should be postponed until after puppies have been weaned.

### **Eosinophilic Meningoencephalitis**

A neurological disorder termed idiopathic eosinophilic meningoencephalitis has been reported in six male dogs, 4 months to 5.5 years of age, in North America [123], and in 3 young male Rottweiler type dogs (between 12 and 17 months of age) in New Zealand [124]. Clinical signs included episodic collapsing into sternal or lateral recumbency without loss of consciousness, depression or somnolence, behavioral abnormalities, loss of learned behavior, circling, pacing, head pressing, blindness, facial palsy, absent gag reflex, reduced menace and pupillary light reflexes, torticollis, incoordination, and generalized or partial seizures. One dog had reduced myotatic reflexes [124]. CSF analysis revealed variable pleocytosis (from 11 to 8,200 WBCs / $\mu$ l) with an eosinophil percentage ranging from 21 to 98. CSF protein content was elevated (range: 19 to 1,430 mg/dl). Three of the six dogs from the initial report were Golden Retrievers. Mild to moderate transient blood eosinophilia was observed in 7 dogs from these two reports. The etiology and pathogenesis of this condition are not known at this time. Pathological studies are limited. In one dog, the cerebral cortex

was atrophied bilaterally, the sulci contained opaque, white exudate, and the meninges over the pyriform lobes were green [123]. Thickening and green discoloration of the meninges was also noted in one of the Rottweilers [124]. Microscopic lesions in the 2 dogs necropsied were almost identical. Severe eosinophilic and granulomatous meningitis, particularly over the cerebral hemispheres, was present, with vacuolation of the underlying neural parenchyma. Other microscopic changes included neuronal pyknosis, mild to severe demyelination of cerebral white matter, and diffuse gliosis and astrocytosis of the cerebral gray matter. Perivascular cuffing was confined to the superficial surface of the cerebral hemispheres. No organisms have so far been seen or cultured. In the original report of this condition, 1 dog recovered with antibiotic treatment (chloramphenicol) and 3 dogs were corticosteroid-responsive [123]. In the Rottweilers, 2 dogs were steroid responsive (1 dog responded quickly while the second responded slowly over a 4 month period and had a relapse) while the third dog showed no improvement and was euthanized [124]. The etiology of this disorder remains unknown, although the presence of eosinophils and the response to corticosteroids suggests an immune-mediated pathogenesis [124]. A similar disorder has been reported in a cat [125]. Clinical signs included nystagmus, facial muscle fasciculations, disorientation, and inability to stand, impaired vision and hearing, brief tonic-clonic seizures, and periodic hypersalivation and facial pawing. CSF revealed a mild pleocytosis (17 WBCs / $\mu$ l), with 81% eosinophils, and mild protein elevation (24 mg/dl). The cat recovered following several weeks of corticosteroid therapy. A type I hypersensitivity reaction was considered as possible cause.

### **Feline Immunodeficiency Virus Encephalitis**

Feline immunodeficiency virus (FIV) (formerly, feline T-lymphotropic lentivirus) is a lentivirus with certain morphological similarities to the human immunodeficiency virus [126]. The neurotropism of this virus has been documented [127] and FIV is considered a useful model for study of human immune deficiency virus infection of the human CNS (neuroAIDS) [128]. It is commonly found in cats with chronic oral cavity infections, chronic upper respiratory tract disease, chronic enteritis, and chronic conjunctivitis [129]. The literature to date suggests that spontaneously occurring FIV causes neurological signs in only about 30% of cats, and the signs tend to be mild or subtle [129-133]. Behavioral changes such as depression, social withdrawal, loss of "toilet-training", unusual aggression, seizures, episodic staring into space, restlessness, disorientation, frequent licking movements, and hyperesthesia are the dominant signs [132,134]. Focal neurological signs, such as head tilt, anisocoria, circling, and spinal cord dysfunction, such as hindlimb ataxia and falling, are infrequently observed, occur late in the disease, and may be associated with secondary opportunistic CNS infections, such as toxoplasmosis and feline infectious peritonitis [132,135]. Histopathological changes in the brain in spontaneously occurring FIV infection include perivascular lymphocytic cuffing, gliosis, and white matter vacuolation [134]. In this report, lesions were most severe in the cerebrum, affecting the white matter and the deep laminae of the gray matter, but were also present in the medulla, and cervical spinal cord. Gemistocytes were prominent, and many bizarre cells with large, sometimes multinucleate, hyperchromatic nuclei were evident. Immunostaining with antibody specific for FIV p24 nucleocapsid protein produced staining in the gemistocytes and glial cells of the white matter. *In situ* hybridization produced staining that was most intense in the white matter and gemistocytes of the deep laminae of the gray matter, thus confirming the infection as active [134].

In experimentally infected cats, subclinical encephalitis has been reported [136], although behavioral changes, anisocoria, delayed righting and pupillary reflexes, as well as delayed visual and auditory evoked potentials, decreased spinal and peripheral nerve conduction velocities, and marked alterations in sleep patterns have been seen [137]. Neurological disease has been observed in both acute and chronic stages of experimental FIV infection [138]. Pathological findings in experimentally infected cats have included diffuse gliosis, glial nodules, occasional perivascular infiltrates, white matter pallor, meningitis, and perivascular leptomeningeal calcification. These changes were seen especially in cerebrocortical white matter and in periventricular locations [136], although early lesions are reportedly located in the basal ganglia and brainstem [132]. A marked increase of glial fibrillary acid protein (GFAP) reactivity has also been noted [131,139]. Experimental studies indicate that the virus targets astrocytes and macrophages [132], may induce microglial activation/proliferation [140], results in delayed neuron loss and axon reorganization, especially in the hippocampus [139,141], and impairs astrocyte homeostasis [142]. Choroid plexus macrophages may contribute to the inflammatory cascade [577]. Systemic immune suppression is also considered an important determinant of FIV-induced neurovirulence [143].

Common hematological abnormalities in cats with naturally occurring FIV infection include anemia, lymphopenia, and monocytosis, along with serum hyperproteinemia, and hyperglobulinemia [130,133]. In spontaneous disease, a mild mononuclear pleocytosis and mild protein increase in CSF may be found [134]. Experimentally, a mild CSF pleocytosis and intrathecal IgG production has been reported [127,144].

A definitive diagnosis of FIV infection can be made by detection of FIV-specific antibodies in blood or saliva. Serodiagnosis for detecting FIV-specific antibodies in serum, plasma, or whole blood presently can be made using a commercial enzyme-linked immunosorbent assay (ELISA), immunofluorescent antibody assay, and a FIV Western blot assay [145]. Prognosis is poor. Safe and effective treatment strategies are presently unavailable [145,146]. Infected cats pose no public health hazard [146].



### **Feline Infectious Peritonitis**

Feline infectious peritonitis (FIP) is a fatal, systemic Arthus-type immunopathological disease caused by feline coronavirus (FCoV) [147-149,578]. Two biotypes of FCoV exist, feline infectious peritonitis virus (FIPV) that causes FIP, and feline enteric coronavirus (FECV) that induces mild enteritis from which cats typically recover [150]. FIPV has been shown to be a mutation of FECV [151] and this virus has the ability to replicate in macrophages, perhaps facilitated *in vivo* by the concept of antibody-dependent enhancement in which presence of antibody to FCoV increases the uptake of virus into macrophages through binding of the antibody-virus complex to the Fc receptor [152,153]. Deposition of virus-infected mononuclear cells and virus-antibody immune complexes within blood vessel walls results in severe vasculitis, with complement-dependent vessel damage and release of cytokines [154,155] leading to serum leakage. There are two clinical forms of FIP:

- a. an effusive ("wet") form resulting from diffuse fibrinous peritonitis accompanied by excessive abdominal fluid [156,157] and
- b. a noneffusive ("dry") form characterized by perivascular granulomas around small blood vessels in various sites, especially meninges, brain and uvea [158].

The effusive form is about four times more common than the non-effusive form. Lesions appear when affected cats mount a vigorous humoral antibody response with very little, if any, cellular immunity [159]. The non-effusive form develops in cats with humoral immunity, but with partial cell-mediated immunity [160]. In other words, this form may represent an intermediate stage of immunity, sufficient to induce granulomatous inflammatory reaction around virus present in macrophages, but not quite adequate to eliminate the infection. Cats who develop a strong cell-mediated and local immune response have the best chance of restricting the virus to intestinal mucosa and mesenteric lymph nodes leading to viral elimination and eventual recovery [161]. Note that in a small proportion of cats there is an overlap of the two forms of FIP [150].

FIP infection has a low morbidity but a high mortality (approaching 100%) [162]. The main route of infection with FCoV is oronasal from contact with infected feces [150]. Asymptomatic carriers are not common [163]. Up to 50% of cats with clinical FIP also test positive for feline leukemia virus [163]. The incidence of FIP is highest in cats 6 months to 2 years of age, although it has been reported in animals as young as 12-weeks of age [164]; lowest in cats from five to 13 years of age; and slightly higher in cats older than 14 years of age [162]. There is no breed predisposition, although results of a recent epidemiologic study indicated that sexually intact male cats may be at increased risk, and spayed females at reduced risk, for FIP [165]. Also, in a study involving Persian cats, cats contracting FIP were all genetically related through the sire [579]. Cats in closed colonies are at highest risk [150,165]. Up to 30% of cats with clinical FIP have CNS involvement [166-168]. The CNS lesions appear to result from an immune-complex-mediated vasculitis. In addition, failure of cellular immunity to destroy the virus results in multiple granulomas, surrounding virus-laden macrophages, within the CNS. Neurological signs and CNS pathology are more often observed in the dry form of FIP [156-158,167,169] however; cats without neurological deficits still may have microscopic CNS involvement [166]. The clinical and neurological vagaries of FIP are recognized in earlier reports and include pelvic limb paresis, generalized ataxia, dorsal thoracolumbar hyperesthesia, nystagmus, anisocoria, behavioral changes, seizures, tetraparesis and intention tremors [166,170]. Multifocal or diffuse CNS involvement is common [171,172]. Animals may show evidence of iritis, anterior uveitis, and chorioretinitis [150].

The pathological findings typical of feline coronavirus disease in the CNS include a pyogranulomatous inflammatory cell infiltration of leptomeninges, choroid plexus, ependyma, and brain parenchyma, although the intensity of the lesions is greatest at the inner and outer surfaces of the CNS [1,158]. Perivascular cuffing and fibrin deposition are prominent. Subependymal periventricular necrosis is commonly observed, as is the infiltration of macrophages, lymphocytes, neutrophils, and plasma cells. Inflammatory ependymal lesions in the aqueduct and central canal may lead to obstructive ventricular dilatation and hydromyelia, respectively [1]. Inflammatory or degenerative vascular changes and thrombosis are sometimes present and many animals have associated panophthalmitis. Several cases of FIP-associated hydrocephalus have been reported [158,166,169,173,174].

Premortem diagnosis, especially in noneffusive FIP, is difficult. It is suggested by clinical signs, including ocular changes (anterior uveitis), laboratory evidence of CSF protein concentration of greater than 2 g/L and a white cell count of over 100 cells/ $\mu$ L (predominantly neutrophils), positive anti-coronavirus IgG titer in CSF, plasma hypergammaglobulinemia, and increased serum fibrinogen levels, and findings on MRI or CT suggesting periventricular contrast enhancement, ventricular dilatation, and hydrocephalus [149,171,172]. High serial serum titers of FCoV antibody may support the diagnosis; however, there is considerable overlap in titers in cats with and without FIP

[175,176] (some cats with FIP have low titers, while many cats with high titers never develop FIP). Furthermore, they have no prognostic value, as they do not appear to be protective [150]. Confirmation generally is made by histopathological examination, either at biopsy or at necropsy. Postmortem diagnosis is facilitated by FIP monoclonal antibody staining of affected tissue and coronavirus-specific polymerase chain reaction [149,177,178]. Hydrocephalus is reported to be a common postmortem finding [172].

The prognosis for clinically affected cats is very poor since most animals die within a few weeks or months [161]. There is no satisfactory treatment and most therapy is based on supportive care, including fluid replacement and nutritional support [150]. The mainstay of palliative therapy is topical or systemic corticosteroids or both [179]. Vaccination using conventional and recombinant vaccines remains controversial since protection is often unpredictable and antibody-dependent enhancement may be seen after challenge [150,153,180]. Results of a recent field trial using modified live virus vaccine suggested that vaccination can protect cats with no or low FCoV antibody titers and that in some cats vaccine failure was probably due to pre-existing infection [181].

### **Feline Leukemia Virus**

A degenerative myelopathy has been reported as a complication of chronic feline leukemia virus (FeLV) infection [532,558]. Affected cats were FeLV antigenemic for more than 3 years. Clinical signs consisted of nonpainful paraparesis progressing to spastic paralysis that sometimes was accompanied by abnormal vocalization and hyperesthesia. No hematological or CSF abnormalities were found and imaging studies (radiography, myelography, or MRI) were negative for spinal cord compressive lesions. Microscopic lesions were found in the spinal cord (especially thoracolumbar) and brainstem and consisted of diffuse white matter degeneration in the absence of inflammation. FeLV antigen (FeLV p27) was identified immunocytochemically in spinal cord of affected cats (in neurons, endothelial cells, and glial cells), while proviral DNA was amplified from sections of spinal cord, intestine, spleen, and lymph nodes. Neuronal and glial infection by FeLV with subsequent axonal degeneration was suggested as the underlying pathogenesis of the CNS lesions in some chronically infected cats.

### **Feline Polioencephalomyelitis**

This is a subacute to chronic, usually progressive neurological disease that has been described in immature and mature cats, of either sex and of different breeds, throughout the world [1,182-184]. The condition known as "staggering disease", a non-suppurative encephalomyelitis with a predilection for gray matter [185,186] may also be included in this group [187]. Overall, clinical signs from various reports have included ataxia with a tendency to stumbling and falling, hypermetria, nystagmus, paresis, circling, opisthotonus, and tonic-clonic seizures. Intention tremors may be seen involving the head. Affected cats are usually mentally alert but some manifest personality changes. Cranial nerve function is normal except for depressed direct and consensual pupillary reflexes in some animals. Postural reactions and segmental spinal reflexes may be noticeably depressed. Occasionally, a localized area of apparent thoracic or lumbar spinal hyperesthesia is evident. In some cases, a psychomotor-like pattern of seizures that is characterized by hallucinations, wild stares, clawing, and hissing and biting at imaginary objects has been reported by owners when cats are asleep. Some cats have fever, leukopenia, myeloid hypoplasia, and non-regenerative anemia. CSF analysis reveals a moderate protein increase and mild mononuclear pleocytosis [187].

Pathological findings are usually restricted to the CNS and are characterized by a disseminated meningoencephalomyelitis. Lesions have a predilection for gray matter and include severe neuronal degeneration and loss with nodular and diffuse astroglial sclerosis, especially in dorsal and ventral horns of the thoracic and/or cervical spinal cord segments, and in the medulla oblongata. Less severe lesions are found in the cerebral cortex, basal and diencephalic nuclei, midbrain, periaqueductal gray matter, and oculomotor and pontomedullary nuclei. Multifocal areas of Purkinje cell degeneration and isomorphic gliosis in the molecular layer of the cerebellar cortex are seen in some cats. Gray matter lesions are accompanied by mild to moderate perivascular cuffing with lymphocytes, focal areas of mononuclear meningitis consisting of multifocal accumulations of lymphocytes, monocytes, and occasionally, plasma cells, and gliosis. Diffuse Wallerian degeneration of white matter (demyelination and axonal necrosis) is usually present in ventral and lateral columns of the spinal cord, as well as along dorsal midline and ventrolateral areas of the medullar oblongata.

The cause of feline polioencephalomyelitis is unknown, although histopathological findings suggest a neurotropic viral infection. Viral inclusions have not been described and attempts at virus isolation have been unsuccessful [182]. The presence of leukemia, myeloid hypoplasia and non-regenerative anemia in some cats suggests possible feline panleukopenia virus infection, which has been known to cause leukodystrophic lesions [188], inflammatory lesions of the brain, and spinal cord demyelination in cats without the characteristic cerebellar lesions [189]. Serological studies have been negative for feline immunodeficiency virus and feline leukemia virus [187]. Another candidate is Borna disease virus. In one study involving 24 cats with "staggering disease", Lundgren and colleagues reported that 44% had Borna disease virus (BDV)- specific antibodies [185,186]. A BDV-like agent was subsequently isolated from the CNS of affected cats [190]. Immunohistochemical studies indicated that T lymphocytes were the predominating inflammatory

cells within the adventitial space, with CD4+ T cells being more abundant than CD8+ T cells [191]. Scattered IgG-, IgA- and IgM-containing cells were found in the adventitial space and surrounding neuropil, often adjacent to neurons. In several cats, BDV-specific antigen was detected in a few cells thought to be macrophages. The successful induction of neurological signs and encephalitis in cats infected with feline BDV, together with the detection of BDV-specific antigen and nucleic acid in the brain of each cat with encephalitis, is strong evidence that BDV is the etiological agent associated with this non-suppurative meningoencephalitis [192]. BDV-specific antibodies have also been detected in German, Austrian, and Japanese cats [193,194].

Prognosis is guarded. Data on treatment are lacking except for the Borna disease cats where supportive treatment, including use of corticosteroids early in the condition (prednisolone at 1 - 2 mg/kg PO divided in 2 doses for 7 days, then gradual reduction over 6 - 8 weeks until 0.125 mg/kg on alternate days) may produce short-term remissions or clinical stabilization [194]. Additional studies should help clarify if other cats in this polioencephalomyelitis grouping belong to the Borna disease group or if they form a subset of non-suppurative meningoencephalomyelitis.

### **Feline Spongiform Encephalopathy**

An encephalopathic neurological disease, termed feline spongiform encephalopathy (FSE), was first reported in 1990 in the United Kingdom [195]. Single cases have been identified in Norway, Ireland, and Lichtenstein [530]. The disease occurs in older cats from 14 months to 14 years of age, with a mean age around 7 years [531]. It does not appear to be related to breed or sex. The condition appears to be related to other transmissible spongiform encephalopathies (or scrapie-like encephalopathies, or prion diseases), such as bovine spongiform encephalopathy (BSE) in cattle, scrapie in sheep, and Creutzfeldt-Jacob disease (CJD) in people. Recent studies suggest that the cases in cats are consistent with oral exposure from consumption of foodstuffs derived from cattle contaminated with the BSE agent which in turn was spread to cattle through animal protein concentrates (e.g., meat and bone-meal) processed from scrapie-infected sheep carcasses [196-200], although long-term experimental studies suggest that some forms of the sheep scrapie agent appear unable to cross the species barrier to produce FSE [559]. There is evidence that the new variant CJD seen in Britain is due to further species-jumping transmission to humans from ingestion of BSE-contaminated beef products [201,202]. The infectious agent in these spongiform encephalopathies is a protease resistant prion protein (PrP), a product of nerve cells, and considered to be an abnormal post-translational modification of a host-encoded membrane-bound cellular glycoprotein produced by infection with scrapie and similar agents that accumulates in the affected brain [196]. The prions are inseparable from infectivity [203]. PrP is also the major protein component of abnormal fibrils (known as scrapie-associated fibrils) that are visualized by electron microscopy [204,205]. These fibrils are found in extracellular deposition of amyloid, seen as plaques or perivascular deposits in sheep with scrapie, which immunostains positively with antisera to PrP [206]. Disease is thought to appear when infectivity and neuropathology have reached a high enough level [201]. The length of the incubation period between the infecting event and the onset of clinical signs may be several years, thus accounting for the disease being observed in older animals. Studies indicate that the nature of the BSE agent remains unchanged when passaged through a range of species, irrespective of their genetic make up, demonstrating that variations in the host PrP gene are not a major factor in the susceptibility to the BSE agent [207].

Neurological signs in cats with FSE are usually insidious in onset and develop progressively over several weeks to months. Signs include muscle tremors, ataxia (especially of the pelvic limbs), dilated unresponsive pupils, jaw champing, salivation, behavioral abnormalities such as uncharacteristic aggression, biting, hyperesthesia, scratching when stroked, creeping about the house and hiding, vacant staring, excessive grooming, and being easily startled by noise. Signs may progress to severe ataxia, dysmetria-hypermetria, sometimes resulting in kangaroo-like movements, and intention tremors of the head. The clinical signs in cats are similar to those described in cats with experimentally-induced Creutzfeldt-Jacob disease [533]. Apart from a moderate leukopenia reported in some cats, laboratory findings are usually within normal limits. Testing for feline leukemia virus, feline immunodeficiency virus, and feline coronavirus is negative.

Microscopic changes in this non-inflammatory degenerative disorder include diffuse vacuolation (single or multiple vacuoles) of gray matter neuropil and neurons throughout the brain, particularly in cerebral cortex, corpus striatum, thalamus, medial geniculate body, and in nuclei of the central gray matter around the mesencephalic aqueduct [195,196,208-210]. Similar lesions occur in the spinal cord. In some instances, neuronal vacuoles are large and extend into axonal processes. These changes are accompanied by moderate to severe gliosis [530]. Perivascular cuffing and/or meningitis are not seen. Vacuolation of the white matter is sometimes seen, especially in the medulla where it is thought to be associated with axonal degeneration in the pyramidal tracts. PrP has been demonstrated in the brains of affected cats (commonly in the gray matter neuropil of the head of the caudate nucleus, putamen, and cerebral cortex [211]) both by immunostaining using the mouse monoclonal anti-hamster PrP antibody [211], immunoblotting, and by detection of abnormal fibrils equivalent to scrapie-associated fibrils using negative stain electron microscopy [209,212]. PrP has also been detected in the myenteric plexus, kidney, spleen, and Peyer's patches of affected cats [213].

There is no treatment. Prognosis is poor, since all spongiform encephalopathy cases are fatal [214]. At this time, there is

no antemortem diagnostic test available. Postmortem diagnosis is made by histopathological examination of the brain. Prevention of exposure to contaminated foods is the most strategic measure. The slaughter of cattle in the UK and the ban on feeding of animal proteins to ruminant species should see the end of the BSE epidemic and also, the 1990s epidemic in cats of transmissible spongiform encephalopathy. There is no direct transmission of the agent between humans and cats. The first case of FSE in a domestic cat outside the UK was reported in Norway that had been fed several imported commercial dry cat food products [211].

### **Granulomatous Meningoencephalomyelitis**

Granulomatous meningoencephalomyelitis (GME) is a sporadic, idiopathic, inflammatory disease of the CNS of dogs and, rarely, cats. This disease appears to have a worldwide distribution, with recent reports coming from the USA, Australia, New Zealand, and Europe [215-223]. GME is thought to account for the majority of lesions previously called reticulosis or inflammatory reticulosis [1,214,224].

The cause of GME is unknown. Bacteriological/mycological cultures of blood and cerebrospinal fluid (CSF) have been negative, as have special agent tissue stains including Gram, Giemsa, Ziehl-Neelsen, periodic acid-Schiff, methenamine silver, and Young's fungal stain. That the lesion resembles experimental allergic encephalomyelitis supports a possible immunological basis for the disease. Immunohistological studies have indicated that many lymphocytic/lymphoblastic cells are immunoglobulin-bearing [215]. The recent report of IgE positive cells (coated mast cells or IgE-producing plasma cells) in perivascular cuffs in 2 dogs with GME lends credence to a possible underlying immunopathological perturbation [225]. In this same study, tryptase-positive mast cells were observed in all 20 dogs with GME and the authors suggested that release of histamine and other bioactive substances by degranulating mast cells may alter vascular permeability and facilitate CNS entry of lymphocytes, thereby contributing to the dynamics of the lesion and to rapid clinical deterioration [225]. Results of an immunomorphologic study further suggested a T cell-mediated delayed-type hypersensitivity of an organ-specific autoimmune disease as a possible pathogenic mechanism for this unique canine brain lesion [226]. It is also possible that GME represents an altered host response to an infectious agent. It is of interest that the onset of signs of GME in two dogs appeared to be related to administration of the anthelmintic drug levamisole, a known immunostimulant [227]. This observation, together with the reported occurrence of CNS lesions in normal dogs after levamisole administration [228], suggested that levamisole might have activated an immune response against latent or incomplete antigens present in nervous tissue. The unusual occurrence of GME in two related Afghan hounds also raised the possibility of common exposure to an infectious agent or genetic predisposition [229]. Summers and colleagues posed the possibility of a retrovirus causing GME, perhaps through vaccine contamination [1]. Distemper and rabies-like inclusion bodies and toxoplasma-like organisms have been described sporadically in CNS lesions of some dogs with GME. However, most GME dogs have been vaccinated against canine distemper and rabies and no correlation has been noted between onset of signs and the time of previous vaccination. Furthermore, canine distemper viral antigen has not been detected in dogs with GME using immunohistochemical techniques [107,225,226,230] and GME occurs in rabies-free countries such as Australia and New Zealand [1]. A recent report suggested a possible etiological relationship with La Crosse virus (see La Crosse virus encephalitis) [543], based on similar pathologic findings.

Most cases of GME occur in small breed dogs, and commonly in terrier and toy breeds and Poodles, although any breed may be affected [216,225,231]. The majority of confirmed cases occur in young to middle-aged dogs, with a mean age around 5 years (ranging from 6 months to 12 years) [231]. GME occurs in both sexes; however, there appears to be a higher prevalence in females [225,231]. The onset of disseminated GME is usually acute, with a progressive course over a 1 to 8 week period [219,220], and dogs with focal GME tend to have a longer clinical course [231]. As a caveat, a lack of obvious correlation between clinical signs and the course of the disease has been reported [225]. Clinical signs usually reflect several (i.e. multifocal) syndromes, e.g., cerebral, brain stem, and spinal cord syndromes, as a result of the scattered distribution of lesions. However, focal signs have been reported in up to 50% of cases [231]. Common signs include incoordination, ataxia and falling, cervical hyperesthesia, head tilt, nystagmus, facial and/or trigeminal nerve paralysis, circling, visual deficits, seizures, depression, and tetanic spasms [221,222,571]. Occasionally, fever, peripheral neutrophilia, and excess non-segmented neutrophils will accompany the clinical neurological signs [219,232]. An infrequently reported ocular form of GME appears to be related to lesions localized in optic nerves and optic chiasm resulting in visual impairment and abnormal pupillary reflexes [233,562]. A hyperemic and edematous optic disk may be seen on ophthalmic examination, vessels may be dilated, and focal hemorrhage may be present [234,235]. Occasionally, ocular and neurological signs may be found together in affected animals.

A tentative diagnosis of GME may be suggested by signalment data, the clinical course of the disease, and clinical signs. Hematology, serum chemistry, and urinalysis studies are usually normal and electroencephalographic recordings are frequently non-specific [225]. Rarely, an intrathecal filling-defect may be detected myelographically in dogs possibly due to focal cord swelling or subarachnoid granulomas [229,230,236]. The most useful diagnostic aid is CSF analysis [220,237]. In most dogs, CSF is abnormal with mild to pronounced pleocytosis, ranging from 50 to 900 WBCs/ $\mu$ l. Cells are predominantly mononuclear, including lymphocytes (60 - 90%), monocytes (10 - 20%), and variable numbers of large anaplastic mononuclear cells with abundant lacy cytoplasm. While neutrophils typically comprise from 1 - 20% of

the cell type differential, they may be the predominant cell type on rare occasions. A marked decrease in CSF cellularity after glucocorticoid administration has been reported by some workers [216,225], but not by others [237]. Protein in CSF is usually mildly or moderately elevated, ranging from 40 to 400 mg/dl. Occasionally, protein is elevated without pleocytosis. In one retrospective study of dogs with GME, lumbar-derived CSF contained fewer cells and less protein than CSF derived from cisternal puncture [237]. CSF protein and cellularity is not necessarily influenced by the degree of meningeal involvement or the extent of necrosis within the granulomatous lesions. Results of CSF electrophoresis from dogs with acute GME have shown the presence of  $\alpha$ -1-globulin and an increase in albumin/ $\alpha$ -1-globulin ratio, suggesting blood-brain-barrier disruption [232]. In chronic cases, an increase in  $\beta$ -gamma globulin values suggests intrathecal production of immunoglobulin [232,238,239]. In addition to an elevated IgG production, evidence of intrathecal IgM and IgA production has been described in several encephalitides, including GME [114]. CSF pressure may be normal or increased. A combination of CSF and MRI findings may also be useful, the latter being characterized by isointense lesions on T1-weighted images [548]. Pial/dural meningeal enhancement may be found with MRI [561]. Although infrequently performed, brain biopsy can be a very useful diagnostic test in animals with focal lesions [231]. Lesions associated with GME are restricted to the CNS. In brain and/or spinal cord, soft, gray, oval lesions with irregular or well-defined margins occasionally can be discerned on gross sectioning, especially with large focal lesions (see below) [218,225,240]. Sometimes, the cut surface of the CNS has a granular, mottled appearance with finger-like projections. Meninges may appear thickened and cloudy, and occasionally, optic nerves are grossly enlarged. Internal hydrocephalus may be present in some dogs. Microscopic lesions are usually widely distributed throughout the CNS, but primarily in white matter of cerebrum, caudal brain stem, cerebellum, and cervical spinal cord. Comparable lesions may be found in gray matter and in leptomeningeal and choroid plexus vasculature. The lesions are characterized by dense aggregations of mesenchymal cells arranged in a whorling perivascular pattern. The perivascular cuffs are composed of histiocytes (a heterogeneous population of MHC class II antigen-positive macrophages) and varying numbers of predominantly CD3 antigen-positive lymphocytes, monocytes, and plasma cells set in nets of reticulin fibers [219]. In some areas, the perivascular cells are predominantly lymphocytic, while in other regions, histiocytic cells are most numerous. Neutrophils and multinucleate giant cells are sometimes present in small numbers. Aggregates of histiocytic cells (granulomatous nodules), sometimes with an apparent epithelioid differentiation [1] appear to develop eccentrically from a previously formed lymphocytic cuff and may also be seen at the center of the most severe lesions. Granulomatous lesions may compress and invade adjacent CNS parenchyma, resulting in necrosis, glial cell reaction, and edema.

Coalescence of granulomatous lesions from a large number of adjacent blood vessels may produce a true space-occupying mass, referred to as the neoplastic form of reticulosis [224]. The dominant reticulohistiocytic cells of this mass may have neoplastic features, such as variable mitotic index and varying degrees of pleomorphism. Focal lesions are usually single and most commonly occur in brain stem, especially in the pontomedullary region, and cerebral white matter. Note that animals with large coalescing granulomatous lesions may also have accompanying disseminated GME lesions [240]. The nature and classification of these so-called "neoplastic reticulosis" lesions remains uncertain. Some cases may be examples of primary CNS lymphosarcomas [215], while others are now thought to be true histiocytic tumors [214] (see also malignant histiocytosis). Large, focal lesions usually produce signs suggestive of a single, space-occupying mass, with signs varying according to the location of the lesion. These lesions can usually be detected using CT or MRI imaging techniques [241].

Prognosis for permanent recovery is poor. Some dogs die from inhalation pneumonia secondary to megaesophagus [230]. Shortest survival periods, ranging from several days to weeks, are seen with the disseminated and ocular forms. Longer survival periods of from 3 to 6 months, or longer, are more suggestive of a focal lesion. In one retrospective study of 42 dogs with GME [231], median survival time for dogs with focal versus disseminated disease was 114 and 14 days, respectively, and dogs with focal forebrain signs (e.g., seizures) had significantly longer survival times (>395 days) than did dogs with focal signs in other areas of the CNS (59 days). Long-term therapy is generally unsatisfactory, although temporary remission of signs is often achieved with corticosteroid administration, such as oral prednisone, 1 to 2 mg/kg/day initially for several days, then reducing the dosage to 2.5 - 5 mg on alternate days. Most dogs will require continued therapy to prevent recurrences of signs. Improvement may last for several days, weeks or months, although most will eventually succumb to the disease [225,231]. Part of the temporary improvement may be related to a reduction of mast cell function in dogs receiving glucocorticoid medication [225]. Cessation of glucocorticoid therapy is invariably associated with rapid and dramatic clinical deterioration. The ocular form of GME may be treated initially with repositol retrobulbar glucocorticoid (betamethasone, 2.5 mg) in conjunction with oral prednisone therapy. Results of a recent retrospective study suggested that radiation therapy (e.g., total doses ranging from 40 to 49.5 Gy, divided in 2.4- to 4.0-Gy fractions) may be an effective treatment for dogs with GME, particularly those with clinical signs suggesting focal involvement [231]. Promising clinical, CT, and CSF results following use of cytosine arabinoside (at 50 mg/m<sup>2</sup>, SQ, bid x 2 days, repeat q 3 weeks) in an 8 year old Shih Tzu [562], suggests that this potent anti-inflammatory drug may be an effective sole therapy for the long-term treatment of GME in dogs.

### **Infectious Canine Hepatitis**

Infectious canine hepatitis is an adenovirus (CAV-1) infection that is a highly contagious systemic disease of young dogs, unvaccinated dogs, and foxes [242,243]. The virus is antigenically and genetically distinct from canine adenovirus 2 (CAV-2), which produces respiratory disease in the dog. The CAV-1 virus is transmitted by direct contact with infected animals (saliva, respiratory secretions, urine, or feces) or by contact with contaminated objects. The virus may also be disseminated by contaminated hands. The virus spreads to local lymph nodes, via the oropharynx, and is disseminated throughout the body by the hematogenous route. There is special predilection for vascular endothelium of liver, kidney, and lymph nodes. The virus may enter the aqueous humor from the blood with subsequent replication in corneal endothelial cells leading to corneal clouding ("blue eye"). As the liver is a primary site of viral injury, signs of acute or chronic hepatitis may be observed. Hepatic insufficiency and hepatic encephalopathy may induce a semicomatose state and death. Signs of encephalitis due to damage of vascular endothelium are rare in the dog; but may include rapidly progressive tetraparesis, coma, seizures and death. These signs may be accompanied by vomiting, abdominal pain, fever and jaundice. Multiple hemorrhages may be present in the CNS, especially in brainstem and caudate nucleus [1]. Perivascular mononuclear inflammatory cells may be seen around capillaries and venules. Characteristic large, amphophilic (Cowdry type A) intranuclear inclusions are present in many tissues, including vascular endothelial cells, and are abundant in liver. Analysis of CSF may show a mild increase in mononuclear cells and protein. Antemortem diagnosis can be obtained by serological testing (e.g., indirect hemagglutination, complement fixation, immunodiffusion, and ELISA), and by virus isolation (e.g., from urine). Prognosis is guarded. Peracutely affected dogs may die within hours of infection. Clinical signs of uncomplicated infectious canine hepatitis frequently last 5 to 7 days prior to improvement [243]. Treatment is symptomatic and supportive.

### **La Crosse Virus Encephalitis**

Sporadic reports of encephalitis have been reported in puppies and in a 4 year old mixed breed dog associated with infection with La Crosse virus (LACV), an RNA *Bunyavirus* (arbovirus) that is spread in the United States by its primary mosquito vector, *Aedes triseriatus* [542,543]. Signs of acute clinical encephalitis included repeated seizures, moribund state, breathing difficulty, and sudden death in puppies, and lethargy, body twisting, falling, head tilt, and seizures in the older dog. Grossly, the brains of affected puppies appeared severely and diffusely malacic. Microscopic lesions were limited to the brain and characterized by nonsuppurative meningitis and multifocal necrotizing panencephalitis, particularly involving the cerebral cortex. Lymphocytes and macrophages were seen in meninges and in perivascular infiltrates within the neuropil. Necrotic areas contained numerous macrophages, variable numbers of neutrophils, and occasional degenerating neurons. No viral inclusions were seen, however, positive immunostaining for LACV was observed in the cytoplasm of monocytes in perivascular cuffs in the older dog. The pathologic changes were considered to be similar to granulomatous meningoencephalomyelitis [543]. LACV in humans also causes an acute encephalitis involving primarily the cerebral cortex (especially the temporal lobe) and mimics herpes simplex viral encephalitis [544]. Interestingly, several children from families living with the older affected dog had recurrent seizures, suggesting possible public health implications.

### **Lyme Borreliosis**

Borreliosis or Lyme disease is caused by the spirochete *Borrelia burgdorferi* which is transmitted to humans and animals by ticks belonging to the *Ixodes ricinus* complex whose distribution is associated with the prevalence of disease, e.g., *I. pacificus* (West coast) and *I. scapularis* (Northeast, Midwest, and Southeast) [244,245]. *Ixodes scapularis* in the Northeast has been previously called *I. dammini*. The tick *Amblyomma americanum* has also been incriminated as a vector. The majority of canine and feline lyme borreliosis cases have been based upon serodiagnosis. In cats, the disease has not been described as a clinical entity [245]. Anorexia, depression, fever, stiffness, joint pain and swelling, and renal disease have been reported in cases of canine lyme borreliosis [246]. Definitive clinicopathological evidence that this organism induces neurological disease in dogs or cats is presently lacking [245], although it has been reported that antibodies against *B. burgdorferi* were found in serum and/or CSF in dogs with undefined neurological disease [247,248]. Intrathecal production of *Borrelia burgdorferi*-specific antibodies by ELISA and Western blot analysis has also been reported in a dog with behavioral changes and seizures [249], but no significant abnormalities were found at necropsy. Further data are needed to clarify the incidence and prevalence of lyme neuroborreliosis in dogs. The organism is sensitive to tetracycline, doxycycline, amoxicillin, ceftriaxone, and imipenem.

### **Meningitis**

Meningitis in dogs and cats is being more commonly diagnosed today compared to the situation 10 to 15 years ago. Several forms of meningitis are recognized.

### **Steroid Responsive Meningitis-Arteritis**

A severe form of steroid responsive meningitis-arteritis (SRMA) has been reported in Beagles, Bernese Mountain Dogs,

Boxers, German Short-Haired Pointers, and sporadically in other breeds. This condition has a worldwide distribution and represents one of the most important inflammatory diseases of the canine CNS [250,251]. Beagles, especially but not exclusively those in laboratory-bred colonies, appear at risk [252-255]. In the Beagles, the condition has been termed Beagle pain syndrome [256], necrotizing vasculitis [257], polyarteritis [258] panarteritis [259], juvenile polyarteritis syndrome [252], and primary periarteritis [260]. In other breeds, this condition previously appears under the terms necrotizing vasculitis [261], corticosteroid-responsive meningitis [262], aseptic suppurative meningitis [263], and corticosteroid-responsive meningomyelitis [264]. This plethora of terminology reflects not only the dearth of knowledge about this condition but also highlights important clinical signs such as pain, improvement following corticosteroid medication, and histologic involvement of the meninges and blood vessels [251].

Affected animals usually are most commonly young adults between 8 and 18 months of age, although the age range may extend from 4 months to 7 years [251]. The clinical course is typically acute with recurrences. A more protracted form of the disease may be seen following relapses and inadequate treatment [264,265]. Signs include recurring fever, hyperesthesia, cervical rigidity, and anorexia. There may be a creeping gait, arching of the back with head held down, and crouched posture [254]. Some dogs with protracted disease may show clinical signs of parenchymal involvement such as ataxia, paresis, tetraparesis or paraplegia. Hematological studies often reveal a peripheral neutrophilia with a left shift, increased erythrocyte sedimentation rate, and in some cases, an elevated  $\alpha_2$ -globulin fraction [251]. CSF studies indicate increased protein and neutrophilic pleocytosis (in some dogs as high as 12,600 WBCs/ $\mu$ m). Dogs with chronic disease may have a normal or mildly increased CSF protein content and a mild to moderate, mixed cell pleocytosis [251]. In acute and chronic forms of the disease, the majority of affected dogs show elevated IgA levels in CSF [265] and serum [252,265], presumably as a result of dysregulation of the immune system. This finding appears to be relatively specific for this disease and is not found in other inflammatory or infectious diseases of the CNS (it may be present in animals with lymphoma, myeloma, or histiocytosis) [251]. Increased CSF levels of IgG and/or IgM have also been noted [266]. Recent studies suggest that the cytokine transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1), does not appear to be correlated with the IgA production [267] and that antineutrophilic cytoplasmic antibodies (ANCA) in serum/CSF are not specific for SRMA [553]. CT imaging may help localize changes in the CNS (meninges, spinal cord, and brain) and assist in the efficacy of therapy [268].

Grossly, subarachnoid hemorrhages may be seen extending over the entire spinal cord and brainstem [1]. Microscopic lesions are characterized by fibrinoid necrosis of the tunica media and vascular thrombosis of vessel walls and periarteritis in the meninges (especially of the cervical spinal cord), cranial mediastinum, and heart [269]. Meningeal fibrosis in some cases may lead to obstruction of CSF flow and hydrocephalus [265]. Partial and complete vessel occlusion by the inflammatory process or thrombi may lead to ischemia. Small and large muscular arteries can be affected. Organization and recanalization of thrombi may be present in chronic lesions [251]. There is extensive perivascular and leptomeningeal infiltration by mononuclear cells (severe lymphoplasmacytic and moderate histiocytic infiltration) plus smaller numbers of neutrophils. In some cases, neutrophils predominate [258,270]. In Beagles, numerous IgG-and/or IgM-containing cells are seen in the leptomeninges and in the adventitia, media, or intima of affected vessels [258,259]. It has been demonstrated that B and T lymphocytes occurred in meningeal lesions, while only T cells were found around inflamed arteries [271]. In animals with parenchymal signs, pathological findings might include subpial wallerian degeneration, nerve root degenerative changes, and rarely, spinal cord infarction or compression secondary to occlusion or rupture and hemorrhage of structurally weakened vessels [270]. In chronic disease, the leptomeninges tend to be thickened with focal mineralization but with milder inflammatory cell infiltration. Amyloidosis (splenic, hepatic, and renal), lymphocytic thyroiditis, and generalized systemic vasculitis are present in some affected Beagles [258,269].

The cause of SRMA remains unknown. To date, no bacterial or viral infectious agents have been identified, although activated T cells have been found in some dogs indicating these cells have had contact with some unidentified antigen [272]. SRMA has the pathological features of an immune-mediated vasculitis [269]. Although deposition of immunoglobulins in blood vessels has not been seen in most studies [1,251,258-260], focal deposits of IgA were found in the vascular wall of one chronic case [266]. It has been reported that in SRMA chemotactic factors are generated in the CNS, including interleukin-8 [273]. The intensity of this production appears to correlate with IgA levels in the CSF suggesting either a causal link or reflecting the severity of the inflammation.

The prognosis is guarded to favorable, especially in dogs with acute disease that are treated promptly using immunosuppressive doses of corticosteroids. Untreated dogs tend to have a remitting and relapsing course [257]. Tipold [251] recommends the following long-term therapy (e.g., for at least 6 months), especially in any dog that has had a relapse: prednisolone at 4 mg/kg/day, PO or IV initially. After 2 days, the dose is reduced to 2 mg/kg daily for 1 to 2 weeks, followed by 1 mg/kg daily. Dogs are re-examined, including CSF analysis and hematology, every 4 to 6 weeks. When signs and CSF are normal, the dose can be reduced to half of the previous dosage until a dosage of 0.5 mg/kg every 48 to 72 hours is attained. Treatment is stopped 6 months after clinical examination, CSF, and blood profiles are normal. In refractory cases, other immunosuppressive drugs such as azathioprine (at 1.5 mg/kg PO every 48 hours) may

be used in combination with steroids (e.g., alternating each drug every other day). Antibiotics are ineffective. Results of a long-term treatment protocol (up to 20 months) involving 10 dogs with SRMA have been recently published [274]. Eight of the 10 dogs were without clinical signs up to 29 months after the treatment was terminated. Long-term glucocorticosteroid treatment resulted only in mild clinical side effects, such as polyuria/polydipsia, polyphagia and weight gain, which were reversible after the therapy was discontinued. It was noted that elevated serum and CSF IgA levels did not decrease to normal values during prednisolone treatment and were still slightly increased after the therapy was discontinued. Monitoring of CSF cell count in dogs with this condition was a sensitive indicator of success of treatment. In addition, older dogs with high IgA levels in the CSF and frequent relapses seemed to require a longer duration of therapy and had a less favorable prognosis long term.

Note that Akitas, Bernese Mountain dogs, and other breeds with immune-mediated polyarthritis may show similar clinical signs as animals with SRMA and have concurrent meningitis [261,275,552].

A case of compressive, cervical, pyogranulomatous inflammation of undetermined cause affecting the dura mater (i.e., pachymeningitis), accompanied by fever and neck pain, right forelimb weakness that progressed to nonweight-bearing lameness and muscle atrophy and proprioceptive deficit has been reported in a 3 year old English Springer Spaniel [276]. Neutrophilia with a left shift was present, along with moderate neutrophilic pleocytosis (43 WBCs/ $\mu$ l) and elevated protein (106 mg/dl) in CSF. Cervical myelography demonstrated extradural cord compression at C4 - C5. Biopsy of the mass revealed marked dural thickening associated with an intense inflammatory cell infiltrate composed of sheets of macrophages and moderate numbers of neutrophils, plasma cells, and lymphocytes. There were also multifocal areas of necrosis and hemorrhage. No organisms were demonstrated. The pachymeningitis ultimately regressed with long-term (over a 30-week period) immunosuppressive therapy that included prednisolone and azathioprine. The authors considered that this case shared features with hypertrophic spinal pachymeningitis of humans, an uncommon, frequently idiopathic, chronic inflammatory disorder causing dural hypertrophy, radiculopathy, and spinal cord compression. It is also possible that the case represents a pathological variant of chronic SRMA.

### **Bacterial Meningitis**

Bacterial meningitis is a rarely reported condition in dogs and cats [1,277]. Animals of any age may be affected, although most affected dogs are adult, with a mean age around 5 years [278]. Bacterial infections of the CNS most often occur via hematogenous spread from distant foci within the body (e.g., lung or splenic abscess, vegetative endocarditis, pleuritis, and urinary tract infections), by direct extension from sinuses, ears and eyes, as a result of trauma (e.g., bite wound), meningeal spread with entry along nerve roots, or from contaminated surgical instruments (e.g., spinal needle) [80,278-283]. Organisms usually disseminate via CSF pathways and produce cerebrospinal meningitis, often associated with microabscess formation of brain and spinal cord. A plethora of organisms have been cultured from dogs with bacterial meningitis including *Pasteurella* sp (e.g., *P. multocida*), *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus albus*, *Actinomyces* sp, *Nocardia* sp, *Escherichia coli*, *Streptococcus* sp (e.g., *S. pneumoniae*) and *Klebsiella* sp.

Bacteria that survive in the circulation enter the CSF from the bloodstream through the choroid plexus of the lateral ventricles and other areas of altered blood-brain barrier (BBB) permeability [284]. Normal CSF contains no phagocytic cells, has a low protein concentration, contains no IgM and is inadequately prepared to counter invading bacteria due to insufficient numbers of complement components and immunoglobulins for bacterial opsonization [285]. The rapid multiplication of bacteria leads to release of bacterial cell wall components and induction of formation of inflammatory cytokines, interleukin-1 and tumor necrosis factor by monocytes, macrophages, brain astrocytes, and microglial cells which leads to further alteration of the BBB permeability, recruitment of polymorphonuclear leukocytes, and formation of a purulent exudate in the subarachnoid space [284]. The permeability of blood vessels increases through the adherence of leukocytes to cerebral capillary endothelial cells, which allows entry of plasma proteins and leads to vasogenic brain edema. Cytotoxic brain edema results from toxic oxygen metabolites released from degranulating leukocytes which have been stimulated by the inflammatory cytokines [286]. Interleukin -1 is thought to play a role in altering the level of consciousness and in fever production by its effect on the hypothalamus. The purulent exudate in the subarachnoid space can interfere with resorptive function of the arachnoid granulations and its presence in the basal cisterns may obstruct outflow of CSF through the ventricles leading to transependymal fluid movement into brain parenchyma and interstitial edema [284]. These mechanism lead to an increase in intracranial pressure and impaired cerebral perfusion pressure (see cranial trauma).

Irrespective of the etiologic agent, bacterial meningitis usually is acute in onset and tends to be characterized by a group of clinical signs that include hyperesthesia, fever, cervical pain, and frequently, cervical rigidity. In addition, vomiting, bradycardia, anorexia, occasional cranial nerve deficits, and seizures may be observed. Seizures may be caused by high fever, hypoglycemia, brain edema, or inflammation, while vomiting may result from increased intracranial pressure or from direct effects on the vomiting center [287]. In some animals, clinical signs may develop that suggest parenchymal involvement. The clinical diagnosis of bacterial meningitis is supported by the finding of highly pleocytic CSF (500 to



1000+ WBCs/ $\mu$ l) with a high proportion of neutrophil cells [288]. The protein content of the CSF is usually increased as well (100 to 1000+ mg/dl). Low CSF glucose, relative to plasma glucose values, are typical. Organisms may be seen on CSF cytology [289]. Neutrophilia may be present in blood samples and there may be evidence of shock, hypotension, and disseminated intravascular coagulation Thrombocytopenia, abnormal liver enzymes, electrolyte imbalance, abnormal anion gap, and uremia have been reported in some cases [278]. Electroencephalographic traces may demonstrate high voltage (30 - 70 $\mu$ v), fast (20 - 35 Hz) or slow (5 - 10 Hz) wave activity. Definitive diagnosis is made by bacterial culture of CSF (both aerobic and anaerobic) [289]. Blood and urine cultures may incriminate a pathogenic organism when CSF cultures are negative (which is usually the case in our experience). Meningeal inflammation, ventriculitis, and possibly brain edema can be detected using MRI or CT scans [278,290].

Pathological findings that are characteristic of bacterial meningitis include diffuse infiltration of inflammatory cells (by both polymorphonuclear and mononuclear cells) into the leptomeninges. Frequently, inflammation is found throughout the entire subarachnoid space of the brain and spinal cord. Vasculitis is often pronounced. Bacterial invasion of CNS parenchyma is characterized by mononuclear and polymorphonuclear inflammatory infiltration and extensive perivascular cuffing. Necrosis of gray and white matter, sometimes associated with vascular thrombosis, may be observed with infiltration of macrophages, neutrophils and plasma cells.

Prognosis is guarded since death is common even if appropriate therapy is administered, and relapses are frequently encountered [291]. Appropriate use of antibiotics, according to the culture results, is basic to successful therapy of bacterial meningitis (encephalomyelitis). Antibiotic therapy should be maintained for several weeks after clinical signs have resolved [277]. Chloramphenicol (up to 50 mg/kg, IV, IM, or SC, bid), metronidazole (10 - 15 mg/kg, PO, tid), trimethoprim-sulfonamide (from 30 to 60 mg/kg, PO, daily; note that complications may include sulfonamide urolithiasis in dogs and nephrotoxicity in cats) penetrate the CNS in therapeutic concentration. Ampicillin and penicillin enter the CNS only with meningeal irritation. Aminoglycosides and cephalosporins reportedly do not adequately penetrate the CNS, even when inflammation exists. Intrathecal administration of antibiotics should only be considered in refractory cases. Corticosteroids, in general, are contraindicated in the treatment of bacterial meningitis [277,291]. It has been suggested that *Staphylococcus* sp. should be assumed when the organism involved is not known [277]. Ampicillin, 5 - 10 mg/kg, IV, every 6 hours is recommended. Diazepam or other anticonvulsants can be used for seizures if they occur. Osmotic diuretics may be useful for treating increased intracranial pressure secondary to brain edema.

Note that it may be very difficult to differentiate between bacterial meningitis and steroid responsive meningitis-arteritis (SRMA). The latter is more common and probably should be at the top of the differential list. Analysis of CSF for elevated levels of IgA should be diagnostic for SRMA.

### **Miscellaneous Meningitis/meningoencephalitis**

Different forms of encephalitis may have an associated meningitis (see Pug dog encephalitis). In general, viruses typically do not produce a pure meningitis. Rickettsial infections (Rocky Mountain Spotted Fever or Ehrlichia) might be considered in dogs with evidence of meningitis and negative cultures (see Rickettsial Disorders). Also, parasitic migration through the CNS can result in aseptic, suppurative meningitis. An eosinophilic CSF pleocytosis may accompany parasitic migration, protothecal infections (see Protothecosis) and some forms of meningoencephalitis in dogs and cats (see Eosinophilic Meningoencephalitis). Trypanosomiasis occasionally may involve the CNS producing a severe chronic meningoencephalitis in dogs. A granulomatous meningitis caused by *Leishmania infantum* has been reported in dogs [570]. Fungal meningitis may be severe, but it is usually associated with granulomatous encephalitis and clinical evidence of parenchymal disease (see Mycotic Diseases). A subclinical encephalopathy associated with feline immunodeficiency virus has a meningitic component (see Feline Immunodeficiency Virus Encephalopathy). Subclinical meningitis or meningoencephalitis may occur in young Akita dogs with polyarthritis [275].

### **Meningoencephalitis in Greyhounds**

An idiopathic nonsuppurative meningoencephalitis in young greyhounds (4 to 18 months of age; male and female) has been reported in Ireland with acute or insidious onset of neurological signs, including head tilting, ataxia, recumbency, circling, depression, and blindness [565]. Microscopic lesions included severe diffuse and focal gliosis and gemistocytosis accompanied by mononuclear cell perivascular cuffing in caudate nucleus and cortical gray matter of the cerebrum and in the periventricular gray matter of the rostral brainstem. Milder lesions were seen in the caudal brainstem, cranial spinal cord, and in the molecular layer of the cerebellum, accompanied by a lymphocyte and plasma cell infiltration of the cerebral and cerebellar meninges. Demyelination, neuropil necrosis, neuronophagia, and vasculitis were not observed. No inclusion bodies, fungi, or protozoal cysts were seen. Serologic and molecular pathology tests failed to determine a cause, suggesting that these cases may represent a novel canine inflammatory disorder.

### **Mycotic Diseases of the CNS**

Mycotic agents sporadically produce a granulomatous meningoencephalomyelitis in dogs and cats. The more common mycotic infections of the CNS are caused by *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Histoplasma capsulatum* and *Coccidioides immitis*. Each agent has a particular geographic distribution in the USA. The pathogenesis

is similar for blastomycosis, histoplasmosis and coccidioidomycosis. The organism is present in the soil, producing mycelia and airborne spores. The coccidia of spores are probably inhaled, deposited in the alveoli, phagocytosed and converted into the spherical parasitic, yeast form. This form is disseminated via lymphatics producing local hilar lymphadenopathy and there is hematogenous spread to other organs. The fate of the infected host is believed to be dependent upon time and ability to develop cellular immunity to fungal antigens. Unlike other mycotic diseases, *C. neoformans* exists only in the yeast form and has a worldwide distribution. Endemic areas have not been identified. Infection is probably acquired from the environment rather than from animals. Cryptococcosis infection often occurs in mature dogs and cats that are immunodepressed (e.g., cats with feline leukemia virus or feline immunodeficiency virus, or dogs with ehrlichiosis), and infection may be accelerated or worsened by glucocorticoid therapy [292]. Cats contract the disease more frequently than dogs. The natural route of infection is generally believed to be the respiratory tract, with subsequent hematogenous and lymphogenous dissemination to other areas of the body. As with bacteria, mycotic infections also may reach brain and spinal cord by direct spread from an adjacent infection, e.g., from the nasal chambers, tooth alveolus and sinuses, outer ear, eustachian tube, middle/inner ear, petrous temporal bone, and basilar bone.

While the overall incidence of CNS involvement by mycotic diseases is low, *C. neoformans* may be more likely to be incriminated than the other organisms in dogs [293-299] and cats [300-303,567]. Neurological signs will vary according to lesion location and severity [303]. The signs may reflect either a focal mass lesion or a diffuse multifocal disease process. Neurological signs may include seizures, depression, disorientation, circling, ataxia, falling, pelvic limb paresis, paraplegia, anisocoria, pupillary dilatation and blindness. Deficits of one or several of cranial nerves 5 to 12 are often present. Note that these signs may be seen with any of the mycotic infections. Radiographic evidence of diffuse miliary to nodular interstitial pulmonary infiltrates may be seen with blastomycosis, histoplasmosis, and coccidioidomycosis. Gross lesions may include thickening of the meninges, which sometimes have a gelatinous, cloudy appearance [302]. On sectioning of the brain, cystic spaces may be seen within the parenchyma. These spaces reflect expanded perivascular spaces and are frequently filled with cryptococcal organisms having a round/ovoid cell body and surrounded by a halo-like capsule that stains strongly with PAS or Mayer's mucicarmine [1]. In cats, only a minimal or mild nonsuppurative inflammatory response may be present. In affected dogs, the cellular response is more granulomatous with epithelioid macrophages, lymphocytes, and plasma cells [295]. The organism may be found as free hyphae or yeast form some of which may be budding. The yeast form is often present within macrophages. Ocular lesions associated with a cell-mediated chorioretinitis may also be observed [304].

Pyogranulomatous encephalitis has been reported occasionally in dogs and cats in association with blastomycosis [305-307]. Neurological disease associated with histoplasmosis and coccidioidomycosis is rare or quite uncommon [1,304,308,309], although granulomatous meningitis attributable to *C. immitis* was diagnosed on postmortem examination in a 4 year old Border Collie by demonstration of coccidioides endospores in brain tissue [310]. There are a few reports of CNS infection in dogs and cats associated with uncommon opportunistic fungi, such as phaeohyphomycoses, in which the agents involved are almost always *Cladosporidium* species, and usually *C. bantianum* [9,311-313]. CNS disease is usually due to localized brain abscess or to multiple large pyogranulomatous lesions in the cerebrum and meninges, sometimes with multifocal malacic foci, and is invariably fatal [314]. Brown, branching hyphae and/or budding yeasts are seen in the areas of pyogranulomatous inflammation [1]. There have been sporadic reports of other fungal infections involving the CNS, including *Geotrichum candidum* (cerebral granulomas, choriomeningitis) [315], *Aspergillus* sp. (cerebral granulomas) [316], and *Paecilomyces* (brain abscess or multifocal perivascular granulomas) [317,318].

Diagnosis of mycotic infection is based on demonstration of the organisms in tissue sections using immunofluorescent procedures or in material taken from aspirates or impression smears, culture, and serology. A commercial latex agglutination test is available for detecting cryptococcal capsular antigen in serum, urine, or cerebrospinal fluid [319]. In dogs, common strains isolated are *C. neoformans* var. *neoformans* and *C. neoformans* var. *gattii* [298]. In one affected cat with cryptococcosis, detailed typing of the strain indicated that it belonged to serotype AD and *Filobasidiella neoformans* var. *neoformans* mating type "alpha" [300]. The agar-gel immunodiffusion test is a useful serological test for diagnosis of blastomycosis. Histoplasma organisms may be found in neutrophils or monocytes of buffy coat or bone marrow smears [320]. Fungal organisms may be observed in CSF (staining is facilitated by using India ink), which usually will be pleocytic (increase in numbers of mononuclear and polymorphonuclear cells) and will have elevated protein levels. Inflammatory mycotic lesions may be detected using MRI, usually as hypointense lesions on T1-weighted images [548], although gadolinium-enhanced T1-weighted images showed multiple, focal contrast enhancing areas in frontal cortex and diffuse meningeal enhancement in one report [299]. In another report involving an 8 year old Chow Chow dog in which an antemortem diagnosis of *C. bantianum* was made using a stereotaxic CT-guided brain biopsy, MRI scans revealed the presence of a large hypointense, irregular lesion corresponding to the location of a phaeohyphomycotic fungal granuloma and pronounced shift of structures toward the midline [313]. Antemortem diagnosis of paecilomycosis in a 3 year old Vizsla was made from a bone-marrow culture [318].

Prognosis of mycotic infection is always guarded, especially in the disseminated form and with CNS involvement. Most of the organisms are sensitive to treatment with amphotericin B (AMB), e.g., using a dosage of 0.1 to 0.5 mg/kg body weight, IV, three times weekly, in dogs and cats [292]. The treatment of choice for cryptococcosis still appears to be AMB and flucytosine (FCY), although toxic epidermal necrolysis may sometimes be seen as a side-effect [296]. A recommended dosage for FCY is 120 mg/kg body weight, divided into 4 equal doses daily [292]. Due to the inability of AMB and FCY to cross the blood-CNS barrier, it is recommended that these drugs be used in combination with other antifungal agents such as itraconazole (ITZ, at 5 - 10 mg/kg, PO, bid) or fluconazole (FCZ, at 5 - 15 mg/kg, PO, bid) [292] in animals with CNS disease. It would seem that the same recommendation would apply to other fungal diseases having CNS involvement, e.g., ITZ at 10 mg/kg, PO, daily is suggested for dogs with blastomycosis/brain involvement [321]. In a recent report of cryptococcosis in 19 cats, treatment with ketoconazole (KTZ), was unrewarding in cases with CNS involvement [303], although KTZ and ITZ (both at 10 mg/kg, PO, daily) successfully treated a small number of experimentally-infected cats, including some with CNS disease [301]. FCZ therapy has been used successfully in a dog for a period of 1 year (before progression of signs and clinical deterioration led to euthanasia) with disseminated CNS cryptococcosis [299] and in cats without CNS disease [322]. FCZ as a sole agent successfully treated an extradural compressive cryptococcal cervical lesion in a 6 year old Doberman [534]. A combination of AMB and KTZ failed to stem the progression of neurological signs (deafness and bilateral vestibular syndrome) in a dog with disseminated paecilomycosis [318].

### Parasitic Encephalomyelitis

In contrast with large domestic animals, myiasis and/or helminthiasis involving the CNS in dogs and cats is infrequently encountered clinically [1]. Most instances of parasitic encephalomyelitis in small animals are the consequence of aberrant migration of parasites that normally reside in dogs and cats, such as *Dirofilaria immitis* or canine *Angiostrongylus vasorum* infestation, although infestation of an aberrant host may also occur, such as the rat metastrongylid *Angiostrongylus cantonensis* which causes paraparesis and ataxia in dogs [323,324]. In general, little is known of the route of migration of parasites that invade the brain, with the exception of hematogenous-borne *Dirofilaria immitis* (heartworm). In Cuterebriasis, caused by the dipteran (fly) parasite *Cuterebra*, larvae possibly gain entry to the cranium by migration through skull foramina, penetration of ethmoid bone and cribriform plate, hematogenous spread after penetrating a large vessel, or via the external-middle ear with direct extension to the meninges and venous sinuses [1,325-327]. Apart from dirofilariasis, which occurs sporadically in mature dogs and cats, CNS parasitic invasion usually takes place in immature and young adult animals that have exposure to the external environment. Some species of *Cuterebra* and some nematodes, such as *Angiostrongylus* sp., may have a selective affinity for the neuraxis and it has been proposed that aberrant cuterebral larval migration in the brain is the cause of feline ischemic encephalopathy [328]. Cysticercosis is another cause of parasitic encephalomyelitis in dogs with sporadic reports coming from Africa, Mexico City, and the United States [329-332]. The larval stage is *Cysticercus cellulosae*, the metacestode of the human tapeworm *Taenia solium* and pigs are the most common hosts. Neurocysticercosis is considered the most common parasitic disease of the CNS in humans [284]. *Toxocara canis*, the common roundworm in the dog, can cause "visceral larva migrans" syndrome in dogs and humans, which may include generalized illness, eosinophilia, and symptoms arising from larval invasion of different organs. Of these, the clinically most important in humans are liver, lungs, eyes and CNS [333]. *Baylisascaris* infection, usually associated with *Baylisascaris procyonis*, the common roundworm of raccoons, sporadically causes cerebrospinal nematodiasis in dogs [334,335]. The epidemiology of this infection appears related to exposure to soil or fecal debris containing contaminated embryonated eggs from caged raccoons shedding large numbers of roundworms in their feces [335]. The larvae may migrate throughout the body, including the CNS. Cerebral coenurus cysts are sporadically reported in cats. These cysts are associated with the larval stages (coenuri) of certain dog tapeworms belonging to the genus *Taenia*, and most reports implicate *Taenia serialis* [336-339]. *Taenia serialis* has a canid-lagomorph life cycle, with cats being accidental intermediate hosts.

Aberrant migration and growth of parasites can result in extensive damage to neural parenchyma which appears to be largely mechanical, although toxic larval excretory products resulting in vascular compromise and ischemia are thought to be important factors in *Cuterebra* infestation [328]. Gross CNS changes in the CNS resulting from parasitic migration may include palpable softening and discoloration of focal areas of the cerebral hemispheres or spinal cord and multifocal presence of small hemorrhages in the cerebrospinal meninges and CNS parenchyma. Microscopic changes are commonly characterized by multiple tracts of necrotic debris, gitter cells, gliosis, vascular rupture with hemorrhage, malacia, and proliferative (granulomatous) changes. The margins of the tracts may have many eosinophilic axonal spheroids, ballooned myelin sheaths, and myelin loss [1]. There may be perivascular cuffs of macrophages, lymphocytes, plasma cells and variable numbers of eosinophils. Parasitic granulomas within the ventricular system, inflammatory changes in the periventricular brain tissue, and stenosis of the mesencephalic aqueduct can lead to obstructive hydrocephalus [340]. Note that it is not uncommon to find parasites in lesion-free areas in paraffin sections, presumably reflecting parasite migration following death of the host [1].

Adult parasites of *Dirofilaria immitis* in dogs and cats usually are found in the right side of the heart and the pulmonary

arteries, but aberrant migration to the CNS occurs occasionally and may cause focal or multifocal cerebral infarction secondary to arterial occlusion, malacic tracts, granulomatous and eosinophilic encephalomyelitis, and parenchymal compression if worms are in CSF pathways [1,341-343]. Aberrant adult heartworm infection resulted in thrombosis of the femoral artery and multiple muscular branches, with subsequent muscle necrosis and inflammation in one hindlimb of a 2 year old Boston Terrier [344]. Additionally, an unusual larval-tissue interaction to microfilariae resulted in a multifocal encephalomyelitis in the brain and spinal cord. In one report of dogs with heartworm microfilarial infection treated with ivermectin, microgranulomas containing microfilariae were found seen in many organs, including skeletal and cardiac muscles, while small glial nodules were seen in the CNS [345]. Angiostrongylosis due to *Angiostrongylus vasorum* occurs in dogs in Europe, especially South West France and the United Kingdom. This worm parasitizes the pulmonary artery and right ventricle of dogs. Just as for *Dirofilaria immitis*, aberrant migration through the CNS by this worm, as well as thromboembolic disease associated with adults or first-stage nematode larvae, may result in neurological disease [346-348]. A rare, aberrant infection with *Ancylostoma caninum* has been reported in a 12-week-old puppy [349], in whom a young adult female parasite was found in the cervical spinal cord in association with severe meningeal and deep tissue hemorrhage. Hemorrhagic and necrotic tracts led from the subarachnoid space to the central gray matter. A granulomatous encephalomyelitis associated with nematode larvae occurs in puppies with neural angiostrongylosis (*A. cantonensis*), with lesion most severe through all levels of the spinal cord, but also extending up to the brainstem [350]. Immature adult worms of *A. cantonensis* have also been identified in brain and spinal cord. In a report of 10 cats with cerebrospinal cuterebriasis, superficial laminar cerebrocortical necrosis, cerebral infarction, subependymal rarefaction and astrogliosis with or without ependymal cell loss, and subpial astrogliosis were seen in addition to the parasitic track lesions [328]. The larvae were recovered most commonly in the region of the olfactory bulbs and peduncles, optic nerves, and cribriform plate, suggesting entry from the nasal cavity. In dogs with cysticercosis, multiple cysticerci (consisting of a fluid-filled cyst in which the invaginated cestode scolex develops) are commonly found in subarachnoid spaces, cerebral cortex, white matter, and ventricles of the brain [329,330]. A chronic inflammatory exudate comprising lymphocytes and macrophages was observed in host tissues surrounding the parasites. In dogs, larvae of *Toxocara canis* may also wander widely through various tissues, including the CNS. Damage may arise from the tracts or from granulomas that develop around larvae whose migration has been arrested. Granulomas comprising inflammatory cells, including eosinophils, and calcified and uncalcified nematodal fragments, have been reported in pituitary gland, brain, and cauda equina of dogs [351]. In one dog, a 2.5 year-old Great Dane, a granuloma consisting of lymphocytes, plasma cells, and occasional eosinophils had destroyed much of the caudal median eminence and adjoining pars tuberalis of the hypothalamus and extended dorsally to involve the ependyma of the third ventricle [352]. In dogs with *Baylisascaris* infection, extensive multifocal necrotizing, granulomatous and eosinophilic encephalomyelitis occurs often with intralesional ascarid larvae [334,335]. Larvae may measure 50 to 70 µm in diameter and often have prominent lateral alae. These larvae are much larger than those of other ascarids, including *Toxocara canis*, and the tissue damage is greater [1]. In cats with cerebral coenuriasis (*Coenurus serialis*, the intermediate stage of *Taenia serialis*), pathology is associated with a fluid-filled cerebral hemispheric coenural cyst (measuring up to 2 cm in diameter) that results in compression of neural tissue with destruction and phagocytosis of neurons and myelin by macrophages (gitter cells), gliosis, and marked perivascular cuffing with lymphocytes and plasma cells [337]. Diffuse flattening of the cerebral hemispheric gyri and obstructive hydrocephalus may occur [339]. The damage from the cyst can be extensive leading to increased intracranial pressure and herniation of the cerebellar vermis into the foramen magnum, and compression of the brainstem and cerebellum [337,339,353].

In animals with parasitic encephalomyelitis, the clinical course may be rapid or chronic, usually progressive, and follows an acute or insidious onset of signs. Clinical signs are extremely variable depending on the location and nature of the lesion. The signs may reflect either a mass lesion in the brain or spinal cord or a multifocal disease process. In dogs and cats with dirofilarial encephalomyelitis, clinical signs may include seizures, visual impairment, constricted pupils, depression, incoordination, circling, paraparesis, or paraplegia [341,344,354,355]. Similar signs may be seen with *Angiostrongylus vasorum* encephalomyelitis [346-348]. Epidural migration of adult heartworms (*D. immitis*) has been reported in several dogs involving cervical and thoracolumbar spinal regions [356-358]. In one dog, signs of a recurring nonambulatory tetraparesis were observed [358]. A 12-week-old Cocker Spaniel puppy with spinal nematodiasis associated with *Ancylostoma caninum* showed signs of incoordination, loss of balance, posterior paresis that progressed to tetraplegia, torticollis, and cervical pain [349]. In a clinicopathological study involving 11 cats with *Cuterebra* larvae myiasis of the CNS, young to middle-aged indoor-outdoor Domestic Shorthaired cats frequently presented with acute neurologic signs that were progressive and most commonly consisted of depression, blindness, and behavior changes [328]. These signs typically occurred from July through September, and many cats had initial clinical signs consistent with upper respiratory disease [359]. In canine neural angiostrongylosis caused by *A. cantonensis*, neurological signs are commonly seen in puppies from 5 to 16 weeks of age and are characterized by a lumbosacral syndrome (paresis or paralysis of tail, pelvic limbs, bladder) that sometimes ascends to involve thoracic limbs, neck, and muscles of mastication [323,324]. Severely affected puppies may become depressed, show behavioral changes, and have seizures. Severe lumbar and/or generalized hyperesthesia is common [360,361]. Neurocysticercosis in a 2 year old Whippet was characterized by a chronic history of falling and circling, difficulty maintaining balance, an inability to walk in a straight

line, and walking sideways [332]. Neurological signs may be minimal in dogs with visceral larval migrans associated with *T. canis* infestation [351], however, hypothalamic larva migrans has been reported in several dogs with diabetes insipidus and signs of polydipsia-polyuria and nocturia [352,362]. Acute signs of ataxia that progressed to recumbency within 48 hours were reported in a 10 week old Walker hound puppy with *Baylisascaris* encephalomyelitis [335], while progressive weakness, dysphagia, and circling were noted in an affected 12-week-old Beagle [334]. Clinical signs in cats with cerebral coenuriasis are extremely variable and may be multifocal if brain herniation has occurred, e.g., ataxic wobbly gait, falling with episodes of extensor rigidity, lethargy, sudden aggression, visual impairment, and depression [337,338,353].

Clinical diagnosis of parasitic migration is difficult but may be suggested by presence of an eosinophilic pleocytosis in CSF (often with neutrophils and mononuclear cells); however, definitive diagnosis requires isolation and/or pathological demonstration of the parasite within the CNS [1]. Signs of ascending paresis/paralysis in young puppies with eosinophilic pleocytosis is considered characteristic of neural angiostrongylosis [323,324]. CSF may be normal in dogs with cysticercosis [332]. Eosinophilia in blood is not considered to be highly suggestive of CNS parasitic migration, since it may also be induced by intestinal worm populations. Epidural heartworms may be detected using myelographic and imaging techniques [356,358]. MRI has been used for the diagnosis of cysticercosis. T1- weighted, contrast-enhanced, 3-mm-thick axial, sagittal, and coronal views of the brain revealed multiple cyst-like lesions located in the subdural portion of the left occipital lobe and the dorsal midline and right dorsolateral aspect of the brain stem [332]. The cysts had high-signal-intensity and ring-like peripheral margins. CT scans have also been used to diagnose coenural cysts in cats [338]. Thrombocytopenia and bleeding episodes associated with chronic disseminated intravascular coagulation have been reported in some dogs with *Angiostrongylus vasorum* infestation [347,363].

Prognosis is guarded and treatment frequently ineffective with most instances of parasitic encephalomyelitis. However, surgical removal of mature heartworms has been successful in several cases of epidural dirofilariasis [356,358], and mildly affected puppies with neural angiostrongylosis (associated with *A. cantonensis*) usually recover with supportive care and corticosteroid therapy [323]. Anthelmintic treatment has been ineffective in this condition and may be contraindicated. In one study, levamisole and mebendazole treatment of dogs mildly affected with neural angiostrongylosis resulted in a 75% death rate [323]. *Angiostrongylus vasorum* in dogs has been successfully treated using ivermectin, fenbendazole, or mebendazole [347,363]; however, severe hypovolemic shock occurred in one dog following levamisole treatment [364], possibly caused by an anaphylactic reaction triggered by the rapid release of a large amount of worm antigen in the blood due to the rapid death of adult worms by levamisole. Treatment of cysticercosis in a 2 year old Whippet with albendazole and prednisone was successful with resolution of clinical signs over several weeks [332]. In endemic areas, environmental sanitation and public education are necessary in order to reduce the incidence of cysticercosis in dogs [329].

### **Parvovirus Encephalitis**

A generalized form of canine parvovirus (CPV-2) infection has been reported in a 7.5 week-old Dalmatian puppy [545]. Histopathological changes in the brain included necrotizing vasculitis, multifocal areas of leukomalacia, and disseminated endothelial hypertrophy in the cerebrum and medulla oblongata. Large basophilic inclusions bodies were observed in some cells of the vascular wall. In sections of the ileum, there was necrosis of crypt epithelium, with dilated, debris-laden crypts typical of the changes noted with canine parvovirus infection. Neurological signs were characterized by sudden onset of circling and blindness. The pathogenesis may be similar to that of feline panleukopenia virus in cats. Parvovirus appears to have an affinity for actively replicating cells. Clinicians should be aware that infection with canine parvovirus may induce neurological signs in addition to enteric and cardiac syndromes. Diagnosis can be confirmed by demonstrating virus or viral antigen in the intestine or feces. A sensitive, in-office test (CITE Test ®) is now available. Several serological tests have been developed. Results of earlier experimental studies suggested that CPV infection potentiates canine distemper encephalitis attributable to modified live-virus vaccine [546].

### **Protothecosis**

Protothecosis is a rare disease caused by an achlorophyllous genus of algae. Two species, *Prototheca wickerhamii* and *Prototheca zopfii*, have been shown to produce systemic disease in animals. CNS involvement has been reported in dogs (but not in cats, in which only cutaneous protothecosis has been observed) with both *Prototheca* sp. [365,366]. The pathogenesis of protothecosis is uncertain. An alimentary route of exposure has been suggested [367,368]. Failure of the host's immune competence (including cell-mediated immunity and impaired neutrophil function) may predispose to infection with this ubiquitous organism. A recent study suggested that either protothecal organisms inhibit the migration or proliferation of cellular inflammatory infiltrates or only dead protothecal organisms induce an effective local immune response [369]. Collie dogs seem to have a higher incidence of this disease compared with other breeds [370]. Infection can occur at any age. Most cases have been reported in female dogs [368]. It appears that the organism has a definite affinity for the eyes in dogs [371,372]. The most common clinical sign is bloody diarrhea. Draining ulcers have been reported only in a few dogs. Neurological signs are variable, reflecting a multifocal disease process, and include visual

impairment, paresis, tetraplegia, deafness, head tilt, facial hypalgesia, anosmia and dementia [367,371,373,374]. CSF abnormalities may include marked pleocytosis (>100 cells/μl) with granulocytes and lymphocytes dominant, and increased protein (>100 mg/dl) [368]. A pronounced eosinophilic pleocytosis (>6,000 cells/μl) and elevated CSF protein (>830 mg/dl) was noted in one dog [366]. Pre-retinal hemorrhage, clouding of vitreous, and multiple white, raised foci or streaks in the retina, and exudative retinal separation have been noted ophthalmoscopically [371]. Organisms have been identified in CSF (e.g., using Gram's iodine stain), in fluid obtained by vitreous centesis, in urinary sediment, and in tissue sections using Gomori's methenamine silver or PAS stains, ultrastructural studies, and immunofluorescence [367,375]. Organisms and pyogranulomatous lesions with neutrophils, histiocytes, lymphocytes and plasma cells, have been described in eyes, brain, spinal cord, kidneys, skeletal muscle, heart, liver, spleen, colon, and lungs [365,366]. Gliosis may be prominent in and around areas of necrosis in the CNS, including gray and white matter. In the spinal cord, scattered demyelinated fibers and swollen axons may be seen, especially in dorsolateral funiculi in cervical and thoracic sections [366]. Small multifocal lesions have been seen in the meninges and ependymal cells lining the ventricles [366]. Organisms have a round to oval shape, range from 10 to 30μm in diameter, and have internal partitions and a birefringent capsule that is PAS positive. Histologically, myriads of protothecal organisms in different stages of development are found in the granulomatous lesions [367]. The prognosis is grave and treatment to date has been unrewarding in dogs with disseminated disease [371,376], although oral ketoconazole for six months resolved most of the clinical signs in one dog with systemic protothecosis and cutaneous lesions [377].

### **Protozoan Encephalitis-encephalomyelitis**

*Toxoplasma*, *Neospora*, and *Sarcocystis* are three genera of the phylum Apicomplexa that cause encephalomyelitis in dogs and cats.

**Toxoplasmosis and Neosporosis** - Toxoplasmosis is an infectious condition caused by the protozoal parasite *Toxoplasma gondii* and occurs in acquired and congenital forms in man and animals [378]. Cats are the definitive host for this parasite. The three known infective stages of *Toxoplasma gondii* are bradyzoites, tachyzoites and sporozoites. The three modes of transmission are carnivorous (ingestion of encysted bradyzoites), fecal contamination, and in utero infection [378]. These modes of transmission involve the different infective stages as follows: carnivorous ingestion of encysted bradyzoites, tachyzoites or both; contamination with feline feces containing sporozoites of sporulated oocysts; transplacental infection of the fetus with tachyzoites after ingestion of encysted bradyzoites or sporulated oocysts by the mother. Humans, sheep, pigs, dogs and (rarely) cats are known to transmit *T. gondii* transplacentally. In humans, congenital infection occurs when a woman becomes infected during pregnancy [379,380]. *Toxoplasma* oocysts are shed in feline feces unsporulated and are not infective until sporulated (1 - 5 days). Sporulated oocysts can survive in soil for several months. Land snails, earthworms, flies and cockroaches may serve as transport hosts for oocysts. Most mammals become intermediate hosts through ingestion of oocysts. Following the acute systemic infection in intermediate hosts in which the organism can be disseminated to many body organs (this phase may be subclinical), tissue cysts form, most commonly in the CNS, skeletal muscle, and heart muscle. This conversion is related to development of the host humoral and cellular immune response [1]. The parasites are mainly intracellular and subclinical infection may persist for the life of the host. Activation of toxoplasmosis may occur in association with severe immunosuppressive disorders [378]. The condition is often associated with canine distemper or other infections such, as ehrlichiosis, or with glucocorticoid therapy [378,381]. Clinical toxoplasmosis is most commonly seen in young dogs less than 1 year of age or in immunocompromised older dogs.

Note that many disorders previously ascribed to toxoplasmosis in dogs have now been found to be cases of neosporosis caused by *Neospora caninum*, an apicomplexan protozoan parasite that can infect puppies in the neonatal period [382-384]. Dogs are the only proven definitive host for *N. caninum* [385,386]. Its life cycle is unknown, although transplacental transmission has been shown in dogs [387-389]. It has a wide host range, but its zoonotic potential is unknown. Older dogs may also be affected [390]. Fatal neosporosis has been documented throughout the world and *Neospora caninum* has been isolated in the USA and in several European countries [391,392]. These isolates may have significant biological and genetic differences [393]. Because many cases of neurological disease previously diagnosed as toxoplasmosis are now turning out to be examples of neosporosis, the acronym TX-NS will be used in the following discussion to encompass both protozoa.

Several clinical syndromes may be observed in dogs with TX-NS infection:

- a. **Encephalomyelitis** - TX-NS in dogs resulting in a systemic infection will typically affect most organs, and the CNS, in particular [394]. Neurological signs associated with TX-NS encephalomyelitis are variable and may reflect a focal or multifocal disease process. In dogs, signs include hyperexcitability, depression, intention tremor, paresis, paralysis, head tilt, and seizures [395]. Clinically apparent encephalomyelitis associated with toxoplasmosis is uncommon in cats; however, pelvic limb paralysis, hypertonia, and hyperreflexia, were observed in a 10 year old, male Domestic Shorthaired cat secondary to myelitis reportedly caused by *Toxoplasma gondii* [396]. The cat was also seropositive for feline immunodeficiency virus, which has been shown to predispose cats to acute generalized toxoplasmosis [397]. Ophthalmic disease, respiratory disorders, muscle hyperesthesia, and fever are common findings in feline toxoplasmosis [398,399]. Note that naturally-occurring cases of neosporosis

have not been documented in cats [400].

Pathologically, perivascular cuffing, diffuse and focal infiltration of meninges by lymphocytes, plasma cells and histiocytes, hemorrhage, edema, necrosis and neuronal degeneration have been described throughout the CNS [401,402]. Protozoan organisms may be found extracellularly and/or in cysts. In one study, tachyzoites (endozoites) within parasitophorous vacuoles were found in neurons, astrocytes, macrophages, and vascular pericytes, while cyst stages were only observed in cells showing features of neurons [402]. Proliferating tachyzoites were associated with lesions of a necrotic-granulomatous type. Activation of astrocytes and perivascular fibroblasts resulted in marked sclerosis. The gray matter was most seriously affected in the brain, while the white matter was most often the site of inflammation in the spinal cord [402]. Experimental infection of kittens with *Neospora caninum* has resulted in fatal encephalomyelitis/myositis [403], although natural infections have not been documented [378]. Congenitally infected children may have signs of retinochoroiditis, hydrocephalus, seizures and cerebral calcification.

- b. Myositis-polyradiculoneuritis - This is probably the most commonly reported infectious myositis in dogs [390,404-408]. The disease tends to be more severe in young dogs, especially those less than 6 months of age. The exact pathogenesis of TX-NS protozoan myositis-polyradiculoneuritis is speculative. While the organisms' predilection for the neuromuscular system is accepted, their myotropism in congenital and chronic infections in dogs remains enigmatic. Protozoan myositis-polyradiculoneuritis in dogs results in progressive pelvic limb paresis, synchronous pelvic limb hopping gait, and bilateral rigidity of the pelvic limbs. Rigid pelvic limb muscles are non-painful on palpation and slowly become atrophic. A fulminating disease resulting in tetraplegia over several days has been observed in mature dogs with TX-NS infection [409]. Extremely severe myonecrosis and mononuclear cell infiltrations were found in all skeletal muscles and protozoan organisms were identified in muscle and CNS. Exacerbations of disease may reflect depression of immune mechanisms in animals with both toxoplasmosis and neosporosis [378]. Pathological changes include variation in fiber size as a result of pronounced fiber atrophy, severe multifocal or diffuse myonecrosis, and mononuclear granulomatous inflammation. Free protozoan organisms are frequently seen within muscle fibers. Interstitial fibrosis is pronounced in chronic cases. In addition, myositis is usually accompanied by nerve fiber degeneration, demyelination, and occasional presence of endoneurial cysts, in nerve roots and peripheral nerves.

In the diagnosis of TX-NS neurological disease, abnormal hematological parameters may include non-regenerative anemia, neutrophilic leukocytosis, lymphocytosis, and eosinophilia. Serum alanine aminotransferase and aspartate aminotransferase levels may be increased, especially in dogs with acute hepatic and muscle necrosis [378]. Results of CSF may be abnormal, with elevated protein content and a mixed monocytic-polymorphonuclear pleocytosis. An eosinophilic pleocytosis was found in 2 dogs with a granulomatous encephalomyelitis due to protozoan infection [123]. Xanthochromia will be present if hemorrhage has occurred. Electromyographic testing may reveal fibrillation potentials, positive sharp waves, bizarre high-frequency potentials, and myotonic-like discharges. Nerve conduction velocities may be decreased. Serum creatine kinase levels are often increased. Protozoan meningoencephalitis has been detected using MRI scans [410]. The close resemblance between *T. gondii* and *N. caninum* tachyzoites and tissue cysts prevents definitive diagnosis by histopathology [384,402], and the clinical syndromes appear to be identical [411]. Differentiation between the two protozoan organisms can be made using assays for circulating antibodies [378,412,413], by tissue immunocytochemistry [414], and ultrastructural studies [401,402]. Sensitive polymerase chain reaction assays have been reported for the detection of both *Neospora caninum* DNA [415,416] and *Toxoplasma gondii* DNA [417] in biological samples. Muscle biopsy of appropriate muscles (as suggested by the clinical signs) may also provide the possibility of a definitive premortem diagnosis using the aforementioned techniques [394].

Prognosis is poor when signs of pelvic limb spasticity are observed [418] and is guarded in any animal with signs of CNS disease. In one study involving 27 cases of neosporosis, recovery was less likely in peracute cases with severe clinical signs, and when treatment was delayed [535]. Many animals with myositis-polyradiculoneuritis have concomitant lesions in the CNS. A 4 to 8 week regimen of trimethoprim-sulfonamide (at 15 - 20 mg/kg combined dose, PO, bid) and pyrimethamine (at 1 mg/kg, PO, daily) has successfully treated animals with TX-NS-induced encephalomyelitis and myositis-polyradiculoneuritis [378,411]. Clindamycin is considered to be the drug of choice for treating canine and feline toxoplasmosis, at a dose of 10 to 40 mg/kg/day, PO or IM, divided bid to tid [378,419]. This dose can also be used for treating dogs with neosporosis [378]. Clindamycin crosses the blood-brain barrier. Oral and parenteral dosages are similar because of the good intestinal absorption of clindamycin [378]. Oral clindamycin can cause anorexia, vomiting, or diarrhea in dogs and cats.

Sarcocystosis - *Sarcocystis canis* has been proposed for the apicomplexan protozoan parasite associated with encephalitis, hepatitis, and generalized coccidiosis in young dogs between 3 and 10 months of age [420,421] in which fatal visceral and neural sarcocystosis has been described [422]. This protozoan parasite is related to *Toxoplasma gondii* and *Neospora caninum*. Only asexual stages of *Sarcocystis canis* are known in macrophages, neurons, dermal, and other cells of the body. The parasite is located free in the host cell cytoplasm without a parasitophorous vacuole. The parasite is PAS-negative and reacts with *Sarcocystis cruzi* antiserum but not with *Toxoplasma gondii* or *Neospora caninum*

antisera, although tachyzoites of these coccidians appear similar in routine HE-stained sections (these organisms can be differentiated ultrastructurally) [420]. In one dog in which there was concurrent canine distemper infection, *S. canis* schizonts and merozoites stained weakly with *Sarcocystis neurona* antiserum [422]. Neurological signs may include depression, generalized weakness, recumbency, nystagmus, periodic seizures, and status epilepticus [420,422]. Microscopic lesions in the brain consist of a subacute or chronic granulomatous meningoencephalitis characterized by vasculitis, malacia, neovascularization, perivascular cuffings, and infiltrations of mononuclear cells and neutrophils [420,422]. *S. canis* schizonts and merozoites may be found in the lesions, commonly within neutrophils and histiocytes. The organisms may also be found in other tissues outside of the CNS.

A *Sarcocystis*-associated meningoencephalomyelitis has been reported in a 13-week-old Burmese kitten with clinical signs of depression, lethargy, crying as if in pain, knuckling of one forelimb that progressed to tetraparesis and a left-sided hemiparesis [400]. Microscopic lesions were confined to the CNS, where a severe meningoencephalomyelitis was characterized by perivascular infiltrates composed of mixed mononuclear inflammatory cells, necrosis of the neuropil, and vasculitis. The most severe lesions were found in the cerebral cortex and caudate nucleus, with multifocal areas of inflammation and associated necrosis, edema, and gemistocytic astrocytosis in the underlying subcortical white matter. Lesions throughout the spinal cord and the medulla oblongata consisted of marked perivascular cuffings of lymphocytes, plasma cells, and mononuclear cells in gray and white matter, with mild inflammatory cell infiltrates in the neuropil. Schizonts and merozoites were found in neurons and in unidentified cells in the neuropil of one spinal cord section. In one neuron, merozoites were seen without a parasitophorous vacuole. The protozoa did not react with antisera to *T. gondii* and *N. caninum* but did react weakly to *S. cruzi* antiserum [400]. In a subsequent report, these organisms were found to react positively to *Sarcocystis neurona*-specific antibodies [423]. Further, cats can act as an experimental intermediate host harboring the sarcocyst stage after ingesting sporocysts [573]. Muscular sarcocystiasis has been reported as an incidental finding in a 9 year old cat [424], while multiple *Sarcocystis* sp. cysts, without any inflammatory response, were found in the muscles of the heart, limbs, diaphragm, eyes and intercostal spaces of a cat euthanized for generalized lymphosarcoma [547].

**Encephalitozoonosis** - Encephalitozoonosis (nosematosis) is a rare disease caused by the opportunistic, obligate intracellular protozoal parasite *Encephalitozoon cuniculi*. This protozoan disease has been reported from many mammals including man, dogs, cats, foxes and laboratory animals [425,426]. It has been reported in Africa, England and in the USA [427-431]. *E. cuniculi* and the related mammalian microsporidia are emerging as significant opportunistic pathogens of immunocompromised individuals [426]. Molecular studies have identified *E. cuniculi* strain III as the cause of encephalitozoonosis in both humans and dogs [432].

Infection occurs by ingestion or inhalation of spores from contaminated urine or feces that are shed by infected hosts, as well as via the transplacental route [433,434]. The organism is shed in urine of affected animals. The condition is typically reported in young puppies, especially those 4 - 12 weeks of age. Bitches producing puppies with overt encephalitozoonosis can be subclinically infected [435]. Clinical signs of disease in young dogs with encephalitozoonosis vary considerably and range from no signs (especially in older dogs) to severe CNS disturbance, coma, and death [433]. Poor growth, ataxia, tremor, blindness, seizures, aggression, and abnormal vocalization have been reported in dogs. In cats, natural infections are rare, but severe muscle spasms, depression, paralysis, and death have been observed [433]. The clinical signs may be identical to those seen with distemper encephalitis in young dogs. Clinical diagnosis can be suggested by a combination of neurological and renal disease in young dogs. It has been stated that experimentally induced disease is invariably subclinical but the histopathological changes are similar although milder than those found in fatal natural disease [436].

Urinalysis can be an indicator of chronic renal disease [436]. Organisms have been identified in urine sediment [433]. In chronic stages, affected animals may have palpably enlarged kidneys, renal anemia and mild to severe increases in creatinine and blood urea nitrogen [436,437]. Lymphocytosis and hypergammaglobulinemia may be present early in the disease. Results of CSF analysis from affected animals are frequently unremarkable, although mild protein increase and pleocytosis may be seen in some dogs, along with higher anti-*E. cuniculi* IgG levels in the CSF than in serum [434]. The prevalence of *Encephalitozoon* antibodies in domestic dogs in South Africa has been estimated at 18% in serological studies using the immunofluorescent antibody test [438]. Both humoral and cell-mediated immune responses develop in dogs experimentally infected with *E. cuniculi* [439]. Reciprocal IgG-immunofluorescent antibody titers >40, or an ELISA titer >1:800 are considered diagnostic of active canine encephalitozoonosis [433,434]. In experimental studies, infected dogs developed an antigen-specific blastogenic response to *E. cuniculi* spores, and lymphocyte blastogenic responses to the lectin phytohemagglutinin A were depressed compared to controls [437]. Definitive diagnosis of this rare disease is based on renal biopsy, routine histopathology, culturing, immunoperoxidase techniques, and electron microscopy [440,441]. Vasculitis is considered to be the basic lesion in canine encephalitozoonosis, frequently leading to thrombosis and encephalomalacia [427]. Vasculitis and fibrinoid necrosis of small to medium arteries are present in brain and viscera. A severe necrotizing nonsuppurative to granulomatous meningoencephalitis, multifocal interstitial nephritis, and glomerulonephritis have been seen in affected puppies [429]. Organisms may be found in neurons and endothelial cells, although viable organisms are present only within endothelial cells. Macrophages containing dead spores are usually seen around parasitized vessels and, less frequently, in the neuropil [427]. Focal hepatitis and interstitial



pneumonitis may also be observed, especially in dogs [436]. In experimental studies, a large component of the inflammatory infiltrate consisted of plasma cells and lymphocytes, and hyperplasia of B-lymphocyte-dependent regions of lymph nodes and erythrophagocytosis were consistently seen in infected dogs [437]. Encephalitozoonosis has been reported in wild dogs in conjunction with intranuclear inclusion bodies in neurons and lesions resembling canine distemper [442]. Prognosis is poor. At present, there is no treatment [434].

**Trypanosomiasis** - American trypanosomiasis is caused by *Trypanosoma cruzi* (canine Chagas disease). This disease is infrequently reported in dogs, and usually in those living in the southern United States [443]. There are presently no reports of domestic feline trypanosomiasis from North America [444]. The main vector is the kissing bug (reduviid vector). Infection usually occurs when trypomastigotes are deposited in the insect vector's feces at bite sites. Oral ingestion of infected insects may also be a route of infection in dogs [444]. Transplacental or transmammary infection is also a possibility [445]. Principal sylvan reservoirs in the USA include opossums, raccoons, armadillos, mice, squirrels, and rats [444].

Clinical signs are most commonly seen with the acute form of the disease (especially in dogs less than 1 year of age) and include lymphadenomegaly, sudden collapse and death associated with acute myocarditis in previously normal young dogs. In some dogs, tachyarrhythmia may be present. More chronic signs include ascites and hepatomegaly associated with right-sided heart failure that will eventually lead to chronic myocarditis with cardiac dilatation [444]. Neurological signs may include weakness and ataxia. A well-studied case report of canine trypanosomiasis due to *Trypanosoma cruzi* involved a 13 month old Doberman Pinscher evaluated because of slowly progressive paraparesis and signs of depression [443]. The dog had temporal, supraspinatus and infraspinatus muscle atrophy, bilateral enophthalmos, superficial inguinal lymphadenopathy, tachycardia with pulse deficits, and lesions of active and inactive chorioretinitis. Neurologic abnormalities included hyperreflexic patellar reflexes, lack of conscious proprioception, and depressed hopping reflexes in the forelimbs. Cranial nerve abnormalities included decreased sensation in the left nostril and a delayed gag reflex [443]. Trypanosomiasis has been reported as an incidental finding in an older dog with laryngeal paralysis [446]. Distemper has been seen in acutely affected puppies [445], possibly as a result of immunosuppression [444]. In experimentally-infected dogs, diffuse granulomatous inflammation, degeneration, and necrosis were observed in the heart, a mild multifocal myositis (comprising mononuclear cells) was present in skeletal and smooth muscle, and a nonsuppurative, lymphohistocytic encephalitis was present along with pseudocysts in the cerebral cortex, cerebellum, and brain stem [447].

Diagnosis may be based on demonstration of trypomastigotes in blood smears from dogs with acute disease (organism are rarely found in animals with chronic disease) [444,446]. Serological tests include indirect immunofluorescent antibody, direct hemagglutination, and complement fixation, with titers becoming positive by 3 weeks post infection [444,448]. CSF analysis may suggest nonsuppurative inflammation [447]. Postmortem diagnosis has been made on identification of the amastigote form of the organism in sections of brain, spinal cord, and myocardium [447]. Organisms are not always present in the brain lesions [449]. The lack of granulomatous myositis and amastigotes in muscle of one affected dog suggested a strain variation in the behavior of *T. cruzi* [446]. Treatment of dogs may be effective using the investigational drug nifurtimox (at 2 - 7 mg/kg, PO, qid, for 3 to 5 months) in conjunction with antiinflammatory doses of corticosteroids [444]. Benznidazole may be effective at 5 mg/kg, PO, daily, for 2 months. Prognosis is guarded. The outcome is usually fatal in chronic cases. Oral cythioate (at 3 mg/kg, every other day) given to dogs housed outdoors will help reduce vector numbers in endemic areas [444].

**Acanthamebiasis** - *Acanthamoeba* is a genus of ubiquitous free-living amebas found in fresh and salt water, soil and sewage [450]. The pathogenesis of acanthamebiasis is unclear, including routes of infection. Amebic meningoencephalitis was reported in a 4 month old female Akita with signs of lethargy, depression, and seizures [451]. The white blood cell count was 7,500/mm<sup>3</sup> and differential count revealed panleukopenia. Gross findings at necropsy included marked vascularity of the meninges and congestion and hemorrhage in the brain parenchyma. The pathologic diagnosis was acute, hemorrhagic, necrotizing and granulomatous meningoencephalitis associated with numerous amebic trophozoites and cysts. Indirect immunofluorescence tests indicated that the amebae were *Acanthamoeba castellanii*. Immunologic studies suggested that the dog was immunosuppressed or immunodeficient which allowed the amebic meningoencephalitis to develop. An outbreak of acanthamebiasis involving grayhounds from 8 to 13 months of age associated with trophozoite and occasional cyst forms of *Acanthamoeba* has been reported [452]. Neurological signs included incoordination, head tilt, ataxia-dysmetria, and seizures. Brain lesions comprised large areas of necrosis and granulomatous inflammation, along with thrombi, hemorrhage, necrosis, and a mixed inflammatory cell infiltrate in the subarachnoid space. Perivascular inflammatory infiltrates were seen in the neuropil mainly composed of macrophages, with a few neutrophils and plasma cells [452]. Contamination was considered to be from a common environmental source. *Acanthamoeba culbertsoni* was isolated from another outbreak of granulomatous amebic meningoencephalitis in a kennel of grayhounds, several of which were affected by a progressive fatal neurologic and respiratory disease [453]. In grayhounds, leukopenia is due to marked lymphopenia [450]. Antemortem diagnosis of acanthamebiasis in dogs is rare, and at present, there is no established treatment, although trimethoprim-sulfonamide at 30 mg/kg, bid, might be effective [450].

**Babesiosis** - Babesiosis is caused by species of the protozoan parasite *Babesia*. Dogs may be naturally infected with *B. canis* and *B. gibsoni*, while *B. felis*, *B. cati*, *B. herpailuri*, and *B. pantherae* are the agents that cause feline babesiosis [454,455]. Under natural conditions, all babesias are transmitted by ixodid ticks. *B. gibsoni* is endemic in the southwestern United States and its vector ticks may be *Haemaphysalis bispinosa* and *Rhipicephalus sanguineus*. Several strains of *B. canis* have been identified, including *Babesia canis vogeli*, the strain commonly found in the USA and in tropical and subtropical regions throughout the world that is transmitted by the brown dog tick, *R. sanguineus*; *B. canis canis*, the European and Asian strain transmitted by ticks of the *Dermacentor* genus, and *B. canis rossi*, the highly pathogenic strain transmitted by *Haemaphysalis leachi* that is found in southern Africa [455]. Transplacental transmission may also occur [455]. In the USA, babesiosis occurs most commonly along the Gulf Coast, and in the south, central, and southwestern states.

Babesiosis in dogs tends to be characterized either by hemolytic anemia or by hypotensive shock and/or multiple organ dysfunction [455]. Clinical signs may include sudden coma and death in hyperacute disease; lethargy, anorexia, fever, and hemolytic anemia, icterus, and splenomegaly, and hypotension in acute disease; and intermittent fever, depressed appetite, and marked loss of condition in chronic disease [454,456]. Fever and icterus are rarely observed in cats, in which signs typically include lethargy, anorexia, weakness, rough hair coat, or diarrhea [455,457]. In animals with babesiosis, CNS involvement is rare; however, seizures, weakness, ataxia, cerebellar signs (e.g., head bobbing, incoordination, head tremors, and variable menace deficits), transient blindness, tetraparesis, and sudden death have been reported sporadically in dogs [458-460]. Clinical signs may be mistaken for rabies. Rare, atypical presentations include *Babesia*-associated muscle tenderness, especially along the back and legs, hyperesthesia including masseteric myalgia which causes dogs to scream with pain if their heads are touched or their mouths opened, rhythmic ear movements, and sciatic nerve peripheral neuropathy [461]. Neurological manifestations may result from sludging of parasitized erythrocytes within capillaries of the CNS with subsequent tissue hypoxia [462]. The molecular mediators of multiple organ dysfunction, including cytokines, nitric oxide, and free oxygen radicals may also play a role [463]. Muscle pain and tremors have been observed in 2 dogs with *Babesia*-associated rhabdomyolysis [464], and muscle necrosis and hemorrhage were present at necropsy.

Primary hematological abnormalities in dogs with babesiosis include anemia, thrombocytopenia, and lymphocytosis. In dogs with rhabdomyolysis, caramel-colored urine and markedly elevated serum myoglobin and muscle enzymes were found [464]. Diagnosis of babesiosis is made by demonstrating the presence of *Babesia* organisms within infected erythrocytes or on positive serology (e.g., using the immunofluorescent antibody test, titers >80 on a single sample are considered positive) [454,455]. The drug of choice appears to be diminazine aceturate [455,460,465]; however, this drug, along with phenamidine isethionate, another very effective drug, is presently not approved for use in the USA. Other antibabesial drugs that are available include pentamidine isethionate (at 16.5 mg/kg, IM, daily for 2 days) and imidocarb dipropionate (at 7.5 mg/kg, IM or SC, single injection) [455]. Prognosis is usually favorable in dogs with uncomplicated babesiosis [455] and dogs with neurological signs may respond favorably to treatment [460]. Prevention measures include environmental control of the tick vector, frequent inspection of skin and hair coat for ticks, application of topical ascaricides (e.g., fipronil) and use of tick collars.

**Leishmaniasis** - This worldwide infectious disease is caused by protozoan organisms of the genus *Leishmania* [582]. The disease is transmitted by sandflies and is frequently seen in dogs, especially in countries around the Mediterranean basin and Portugal. The condition is rarely encountered clinically in cats. Cutaneous (symmetrical alopecia and dry desquamation over the head/body, with or without ulcers) and visceral involvement (weight loss and muscle atrophy) may be seen. Although organisms have been identified within the CNS [583,584], neurological signs are usually not apparent. A granulomatous meningitis caused by *Leishmania infantum* was reported for the first time in 2 naturally infected dogs [570]. The lesions were characterized by lymphoplasmacytic infiltrates and the presence of large numbers of parasites (amastigotes) within macrophages. Clinical signs included lethargy, paresis, and cervical rigidity. Anti-*Leishmania* antibodies were detected in sera and CSF. Note that Leishmaniasis is an important zoonotic disease. A myositis caused by *Leishmania infantum* is also well recognized in Europe (see Infectious Myositis).

### **Pug Dog Encephalitis**

A sporadic, necrotizing meningoencephalitis affecting juvenile, adolescent, and mature Pug dogs of either sex has been reported in the USA, Australasia, Southeast Asia, and Europe [1,466-471]. Dogs range in age from 6 months to 7 years and many affected dogs are closely related and/or born in the same kennel [467]. Onset of signs is frequently acute. The course of the disease varies from several days to 6 months or more. Common clinical signs include seizures, depression, staring into space, circling, head-pressing, blindness with normal pupillary reflexes, strabismus, cervical rigidity, opisthotonus, and intermittent screaming. Death is often preceded by coma or status epilepticus. In a 2 year old dog, visual hemifield loss (homonymous hemianopia) preceded onset of neurological signs [472]. CSF shows moderate to marked mononuclear (usually lymphocytic) pleocytosis (70 to 600 WBCs/ $\mu$ l) and moderate protein increase (58 to 228 mg/dl). Results of hemograms, blood chemistries, and urinalysis are normal. MRI studies on one affected 3 year old dog revealed dilated cerebral ventricles and inflammatory lesions throughout the cerebral hemispheres [473].

Macroscopically, cerebral gyri may appear flattened and multiple variably sized (e.g., 0.2 - 0.5 cm in diameter) yellow-tan foci may be seen within the cerebral hemispheres involving both white and gray matter [474]. Cortical lesions are typically bilateral, asymmetrical, and often confluent. Subcortical white matter is frequently involved, especially areas in the centrum semiovale and corona radiata where there may be loss of distinction between gray and white matter [1]. In one report, the lesions were most extensive in the ventral cerebrum, especially in the parietal and occipital regions [474]. Lateral ventricular dilatation has been observed in one dog [475]. Microscopically, a non-suppurative meningoencephalitis is seen mainly restricted to the cortical leptomeninges (especially in sulci) and cerebral hemispheres and characterized by perivascular accumulations of lymphocytes, plasma cells, and macrophages, neuronal necrosis, and focal malacia, sometimes with cavitation. Hypertrophy and hyperplasia of endothelial cells may be prominent. Lesions in white matter include edema, glial necrosis, reactive astrogliosis, loss of myelin staining, perivascular cuffing, and axonal degeneration. Perivascular cuffs and radiculitis may be present in trigeminal ganglia. Minimal lesions are seen in brainstem or spinal cord. Myocardial necrosis has been reported in one affected Pug dog [474] while echocardiography and pathological examinations have identified a ventricular septal defect and double-chambered right ventricle in another Pug [476].

The etiology is presently unknown; although alpha type herpesvirus encephalitis has been suggested as a possible cause, based on the extensive necrosis and affinity for the cerebral hemispheres [467]. However, subsequent virus isolation attempts have been negative [1]. In one report, all 3 affected animals were females with clinical histories of pregnancy or pseudopregnancy 2 weeks or less before the onset of the clinical signs [468]. An autoantibody against GFAP (glial fibrillary acid protein)-positive astrocytes and their cytoplasmic projections has recently been identified in CSF and serum of several affected dogs [477]. While the role of this autoantibody for astrocytes remains to be defined, it may prove to be a useful clinical diagnostic marker and a key to the pathogenesis of this disease. Prognosis is poor. Seizures are often refractory to anticonvulsant drugs [475], and corticosteroids are ineffectual.

A similar condition has been reported in Maltese dogs in which the clinical course and pathologic changes are indistinguishable from necrotizing meningoencephalitis of Pug dogs, indicating that this lesion is probably not unique to Pug dogs [478]. In addition, similar histopathological lesions have been recently reported in a 4 year old male Pekingese dog with a history of recurrent seizures and progressive abnormal gait and behavior, which did not respond to treatment [479].

Multifocal non-suppurative necrotizing encephalitis has also been observed in Yorkshire terriers in Switzerland [480]. Clinically, the dogs presented primarily brainstem signs or evidence of cerebral involvement, including seizures. The course of the disease was mostly chronic and progressive. Protozoal, bacterial and mycotic organisms were not found on histopathological examinations. The morphology of the lesions was strongly suggestive of a viral etiology, however, immunocytochemistry and/or *in situ* hybridization failed to provide evidence for canine distemper virus or canine herpesvirus infection. Other known canine encephalitides were excluded on clinical and morphological grounds, although there were certain similarities to Pug dog encephalitis. The necrotizing encephalitis reported in a 10 year old spayed female Yorkshire terrier in the USA [481] appears to be more related to the cavitating, necrotizing encephalopathy described in Yorkshire Terriers.

### **Pyogranulomatous Meningoencephalomyelitis**

Pyogranulomatous meningoencephalomyelitis is an acute, rapidly progressive disease of two to three weeks' duration that (to date) has been recognized only in mature Pointers [80]. The cause of the meningoencephalomyelitis is unknown. Special histological stains for microorganisms, cultures of blood and cerebrospinal fluid (CSF), and studies of animal inoculations have all been negative. Clinical and pathological data suggest a bacterial etiology. Clinical signs include cervical rigidity, kyphosis, nose held close to the ground, reluctance to move, incoordination, head tilt, falling/rolling, spontaneous and positional nystagmus, and seizures. Occasionally atrophy of the cervical muscles, facial paralysis, Horner's syndrome, bradycardia, and vomiting are observed. Pathological findings are found throughout the brain and spinal cord, but are most severe in the upper segments of the cervical spinal cord and in the lower brain stem. These changes are characterized by extensive mononuclear (plasma and lymphocytic cells) and polymorphonuclear inflammatory infiltrations in the leptomeninges and parenchyma. Large perivascular cuffs are seen. In some cases, central necrosis of gray matter and edema are found in segments of the cervical cord along with infiltration of macrophages, monocytes, neutrophils, and plasma cells. These changes are probably secondary to impaired spinal circulation from the meningeal reaction. An increased population of reticuloendothelial cells is occasionally observed among the perivascular cells. Focal ependymitis may be present along ventricular pathways. Marked, predominantly neutrophilic pleocytosis (500 to 1000 WBCs/ $\mu$ l) and an increased protein concentration (sometimes over 700 mg/dl) are found on CSF examination. In this small series of cases so far observed, prognosis has been poor. Temporary remission of signs has resulted following antibiotic therapy.

### **Rabies**

All warm-blooded mammals are susceptible to rabies encephalitis and there is considerable interspecies susceptibility. Rabies is the most important zoonotic infection. Wildlife are the chief natural reservoir of rabies [482,483]. In most

northern countries such as Continental Europe, Canada, Greenland, and the former Soviet Union, foxes are the main vectors and also reservoirs [484,485]. In other parts of the world, wolves (Iran); mongooses (the Caribbean); skunks and raccoons (USA); and bats (Latin America) play important roles in transmitting rabies [486]. The dog remains an important vector for transmitting rabies to humans in developing countries [487]. In the USA, dogs play a relatively small part in current epizootics. Vaccination of dogs helped to bring down cases of canine rabies in the USA from 5000 cases in 1946 to 338 cases in 1987, thus eliminating the major route of rabies transmission to people. Presently, rabid cats account for a greater proportion of human rabies post-exposure prophylaxis than do rabid dogs [488]. A recent report indicated that bat-associated rabies virus variants were not a common cause of rabies in dogs and cats in the USA [489]. In contrast, bats have been implicated in most recent cases of human rabies in the USA [490]. Rabies is caused by a rhabdovirus (genus *Lyssavirus*) that is destroyed by lipid solvents and low pH [491]. Transmission most often occurs through bite wounds from infected animals that are secreting virus in their saliva. Infection may also occur by wound/abrasion contamination from infected saliva or other infected material, or by airborne transmission (e.g., in bat caves where the density of virus particles is high) and infection through mucous membranes. The incubation period is variable, depending on the amount of virus transmitted, site of inoculation (e.g., bites closer to the head have shorter incubation periods than those at the periphery), viral strain, immune status, and nature of the wound. In naturally occurring cases of rabies, incubation periods may range between 3 weeks to 6 months in dogs, 2 to 6 weeks in cats, and 3 weeks to 12 months in people before CNS signs are seen [492]. After an early replicative phase in striated muscle [493,494], rabies virus is highly neurotropic and reaches the CNS via passive centripetal movement in the axoplasmic compartment of motor and sensory peripheral nerves. Following the entry of the virus into CNS, usually spinal cord, its ascending course to the brain is rapid (possibly via CSF pathways). The virus has a significantly higher tropism for neurons than for glia [495]. The virus may also pass from neuron to neuron via synapses [1]. Once the CNS has become infected, virus spreads centrifugally via peripheral nerves (sensory, motor, and autonomic) to other organs, including the eyes, salivary glands, and skin. Salivary gland mucous epithelium is the major source of virus shed into secretions in species that maintain rabies in nature. These include the dog, fox, skunk, raccoon, and bat [496]. Presently, in cases of suspected rabies, a holding period of 10 days is recommended. However, results of experimental studies indicate that dogs can excrete rabies virus in the saliva up to 13 days before clinical signs are exhibited [497]. Thus, a longer observation period (e.g., 3 weeks) seems more appropriate.

Initial clinical signs tend to be nonspecific and include apprehension, restlessness, anorexia, and vomiting. A change in temperament may be noted at this stage and excessive salivation may occur. These signs, which may be present for 2 to 5 days, are followed either by the dumb or the furious form of the disease. Approximately 25 - 30% of affected animals exhibit the furious form, which is characterized by increased restlessness, wandering, viciousness (attacks on animals, people, or inanimate objects), howling, polypnea, drooling of saliva, and sometimes convulsions [498]. Furious rabies is associated with infection of limbic system neurons [499]. Death usually occurs between four and eight days after the onset of clinical signs. It is usually the furious form of rabies that occurs in cats. The dumb or paralytic form of rabies encephalomyelitis is more common in dogs and is characterized by progressive ascending spinal paresis or paralysis, paralysis of the lower jaw, pharyngeal and hypoglossal paralysis (resulting in difficulty in eating and drinking, and drooling of saliva), and facial paralysis. Biting is uncommon with this form of rabies. In dogs, a noticeable change in the character of the bark occurs as a result of laryngeal paralysis. Death from respiratory failure occurs between 3 and 6 days after the onset of clinical signs. A moderate mononuclear pleocytosis (40 - 60 WBCs/ $\mu$ l) and slight protein elevation (50 - 70 mg/dl) may be found on CSF analysis in dogs and cats.

Pathologically, rabies is characterized by a multifocal, mild, polioencephalomyelitis and craniospinal ganglionitis with mononuclear perivascular infiltrates, diffuse glial proliferation, regressive changes in neuronal cells, and glial nodules [1]. There is no apparent correlation between the severity of changes and the clinical signs observed. In people and animals, rabies virus is usually extremely widespread in the brain. There is a predilection for the brain stem, especially the substantia nigra, red nucleus, and periaqueductal gray matter of the midbrain; the pontine nuclei; the reticular formation; the floor of the fourth ventricle; and the hypothalamus. Other areas commonly affected include the gray matter of the spinal cord, hippocampus, globus pallidus, and thalamic nuclei. Intracytoplasmic Negri bodies (viral antigen aggregates) are usually most numerous in hippocampal neurons and Purkinje cells. Many cells with inclusions remain morphologically normal. The frequency of Negri bodies is often inversely proportional to the severity of inflammation [1]. Not all rabid animals have inclusions, including animals killed early in the course of the disease [1]. The inclusions need to be differentiated from the pseudo-inclusions seen in neurons of the lateral geniculate nucleus and hippocampal pyramidal cells of cats [500] and neuronal cytoplasmic lamellar bodies seen in nonrabid dogs (especially in thalamic and cerebellar Purkinje neurons) [501,502]. The lamellar bodies are stacks of parallel cisternae derived from endoplasmic reticulum [502] and can be differentiated from Negri bodies using immunoperoxidase staining and/or fluorescent antibody staining techniques [501]. Ultrastructurally, rabies virus particles are characteristically bullet-shaped and embedded in an amorphous matrix [487].

It should be noted that clinical signs associated with rabies in dogs are often so variable that a distinction between the

furious and dumb forms may be unjustified [503]. As a result, the diagnosis of rabies must be based on laboratory confirmation-histopathological examinations of brain sections/smears for presence of an acute meningoencephalitis and identification of Negri bodies; direct immunofluorescent antibody test on tactile facial hair follicles obtained by skin biopsy or on fresh or frozen brain samples, and mouse inoculation. Mouse inoculation has the disadvantage of a 3-week observation period to establish a negative diagnosis. The rabies immunofluorescent antibody test is widely used, for it is an extremely accurate and rapid technique. Also, a focus-forming inhibition assay to detect rabies antibodies in serum is available. Rabies viral antigen can be shown immunocytochemically as well as through use of the fluorescent antibody test in formalin-fixed, paraffin-embedded tissue [1,504]. Antigenic differences between rabies strains have been documented using monoclonal antibody studies [505,506]. A rapid diagnostic technique based on amplification of nucleic-acid sequences to detect rabies-specific RNA in the saliva and CSF has been reported in human patients with rabies [507]. In addition, single-tube, non-interrupted reverse transcription-polymerase chain reaction for the detection of rabies virus in brain tissue has been recently published [508].

There is no treatment. Animals exposed to rabies that have not been immunized should be euthanized. If the animal is current on rabies vaccination and exposed (and the owners do not want euthanasia), the animal should be revaccinated and closely confined under observation for at least 3 months. Administration of a potent vaccine, as a booster after exposure in previously immunized animals, results in rapid amplification of the antibody titer.

Note that **post-vaccinal rabies** occurs occasionally in dogs and cats [509,510], especially if vaccination is done at a time of stress, e.g., surgery. It has been reported that monoclonal antibodies can be used to confirm vaccine-induced rabies in dogs and cats [511]. There have been a few reports of animals recovering after street virus and vaccine virus-induced rabies [487,509,512]. These findings place an increased responsibility on the veterinarian in managing animals with encephalomyelitis.

### **Rickettsial Meningoencephalitis**

Rickettsial diseases such as Rocky Mountain spotted fever (RMSF) caused by *Rickettsia rickettsii*, and canine ehrlichiosis caused by *Ehrlichia canis* (canine monocytic ehrlichiosis) sporadically involve the CNS of dogs, where they produce a meningoencephalitis [513-515]. Several other granulocytic ehrlichial species, in which the morula inclusions are primarily in neutrophils, such as human granulocytic ehrlichiosis (HGE), *E. equi* (equine granulocytic ehrlichiosis), and *E. ewingii*, may also cause CNS signs in dogs [515,516]. In contrast, a recent experimental study in which dogs infected with either *E. canis*, *E. ewingii*, *E. chaffeensis*, or HGE, indicated that ocular (uveitis) and brain lesions (meningitis) were observed only in dogs infected with *E. canis* [517]. Ehrlichiosis and RMSF are tick-borne disorders. *Dermacentor andersoni* and *Dermacentor variabilis* are the primary vectors for RMSF in North America. The arthropod vector and primary reservoir for *E. canis* is the brown dog tick, *Rhipicephalus sanguineus*. Canine RMSF occurs mainly in the spring and summer. In both diseases, vasculitis and perivascular inflammatory cell infiltrates may be observed in most body tissues. CNS lesions are characterized by a lymphoplasmacytic meningoencephalitis involving the meninges, cerebral cortex and brainstem. Both diseases are characterized by fever, depression, and lymphadenopathy. Edema may be seen on the lips, penile sheath, ears, and limbs. Neurological signs occur in about one third of dogs with either RMSF or ehrlichiosis and include seizures, depression, paraparesis or tetraparesis, vestibular dysfunction, generalized or localized hyperesthesia, cranial nerve deficits, intention tremors of the head, and coma [514,518,519]. Fundic lesions, including retinal hemorrhage, chorioretinal exudate, or retinal detachment can occur with either disease [520]. Hyporeflexia, tetraparesis, and muscle wasting associated with lymphoplasmacytic polymyositis were seen in 2 dogs seropositive for *E. canis* [521]. Analysis of cerebrospinal fluid (CSF) from dogs with either disease may reveal slight to moderate elevations in protein content (e.g., 40 to 160 mg/dl) and variable, predominantly mononuclear pleocytosis (10 to 130 WBCs/ $\mu$ l). Thrombocytopenia occurs with both diseases, often accompanied by anemia, hypoalbuminemia, leukopenia early in the disease followed by leukocytosis, and hyperproteinemia. Coagulation abnormalities may be present [522]. Intracytoplasmic ehrlichial morulae may be observed in blood leukocytes, especially monocytes, and in CSF mononuclear cells. A four-fold rise in antibody titer to *R. rickettsii*, or a single *R. rickettsii* antibody titer of 1:1,024 or greater (when this initial titer is determined one week or more after the onset of clinical signs), or positive direct fluorescence for *R. rickettsii* in skin biopsy specimens will confirm a diagnosis of RMSF [523]. The latter technique can confirm the diagnosis as early as the 3rd or 4th day of disease on a single sample [524]. Recently, elevated platelet-associated immunoglobulin titers have been reported in dogs with RMSF [525]. A single positive serum titer, using the indirect FA test for *E. canis* is considered indicative of infection, since animals become seronegative within 3 to 9 months after effective treatment. Most laboratories measure IgG and a titer  $\geq 20$  is generally considered to be evidence of infection and/or exposure [515]. Note that there is some antigenic cross-reactivity between ehrlichial species [515].

The treatment of choice for both diseases used to be tetracycline, using a dosage of 22 - 30 mg/kg, PO, tid; although the newer semisynthetic, lipid-soluble tetracyclines, doxycycline (at 10 - 20 mg/kg, PO bid) and minocycline (at 3 mg/kg, PO, bid) are used more frequently now [515]. Chloramphenicol may also be used at 15 - 30 mg/kg, PO, tid. Traditionally, animals are treated for 14 to 21 days. Chloramphenicol is recommended for use in puppies less than 6 months of age to avoid tetracycline-induced discoloration of permanent dentition. Antibiotics are only effective in

reducing the severity of infection if given early in the course of the disease [515,524]. While dogs without neurological disease can show a dramatic response to treatment, generally within 24 to 48 hours [526], the prognosis is guarded for those animals with neurological signs. Recovery may be prolonged with residual neurological deficits from irreversible brain damage. It has been reported that dogs with RMSF have a more rapid and consistent recovery than dogs with ehrlichiosis in the absence of neurologic deficits and when treated with tetracycline [514].

Prevention measures include environmental control of the tick vector, frequent inspection of skin and hair coat for ticks, application of topical acaricides (e.g., fipronil) and use of tick collars [524]. Tetracycline at 6.6 mg/kg PO, daily, is an effective prophylactic drug against initial infection or reinfection with *E. canis* [515]. Note that RMSF is an important zoonotic disease [524]. It now seems that dogs and cats can be naturally infected with the granulocytic strains *E. equi* or *E. phagocytophilia* which may cause HGE in people, although the role, if any, of domestic animals in the human disease is yet to be determined [515,527]. Ehrlichiosis has been reported in cats [515] but the species have yet to be identified and, to the author's knowledge, signs of CNS disease have not been described.

### Salmon Poisoning

Salmon poisoning, caused by *Neorickettsia heminthaeca*, is a lethal rickettsial disease of dogs on the Pacific West Coast. Infection is acquired by eating salmonoid fish, certain species of nonsalmonoid fish, or the Pacific giant salamander that contain metacercariae of the fluke *Nanophyetus salmositica*, which harbors the rickettsiae throughout its life cycle stages from egg to adult. Snails and then fish serve as intermediate hosts for the flukes [528]. The infection in dogs results in a subclinical diffuse mononuclear leptomeningitis [1].

### Shaker Dog Disease

This condition has been observed in the United States and Australia involving young, mature dogs of either sex. It has been noted particularly in Maltese and West Highland White Terriers, although the condition has also been seen sporadically in Bichon Frise, Spitz, Samoyed, Beagle, Dachshund, and Yorkshire Terrier dogs [536-539]. In a recent report of 24 dogs with generalized tremors (2 of which were associated with mycotoxin ingestion), most were young adults between 1 and 5 years old, more than half of the dogs were nonwhite mixed-breeds, and all weighed <15 kg [540]. Synonyms for this disease include idiopathic tremors of adult dogs, sporadic acquired tremors of adult dogs, and "little white shakers" since many dogs are white. The underlying pathogenesis remains unclear; however, an acquired autoimmune disorder affecting neurotransmitter synthesis (dopamine, epinephrine, and norepinephrine) has been hypothesized [536].

The tremors appear to be intentional and worsen with exercise, stress and excitement, and disappear with sleep. Signs may occur sporadically, progress over 1 to 3 days, and remain static. Occasional dogs have a history of spontaneous clinical improvement [538]. Tremors typically involve all four limbs and the head. The eyes may also be affected. Neurological examination is usually normal; however, absent menace response, nystagmus or dysconjugate eye movements, ataxia, head tilt, tetraparesis, and paraparesis were variably noted in a report of generalized tremors involving 7 Maltese dogs [539]. Mild to moderate hypermetria and body swaying may also be present. Rarely, seizures are seen. Results of hematological and serum biochemical testing and urinalysis are usually within normal limits, although peripheral eosinophilia was found in 3 dogs in one report [539]. CSF analysis often reveals a mild to moderate lymphocytic pleocytosis, usually with normal or mildly elevated protein levels. MRI scans have demonstrated symmetrical ventricular enlargement in some dogs [539]. In this report, abnormal electroencephalographic traces were characterized by either generalized low-frequency (6 to 9 Hz) high-amplitude (25 to 100  $\mu$ V) activity or low-frequency (7 to 9 Hz) normal amplitude (10 to 25  $\mu$ V) activity. Brainstem auditory evoked response testing showed mildly increased I to V or I to Vn waveform latencies [539]. Histopathologically, a very mild diffuse, nonsuppurative encephalomyelitis, with perivascular cuffing by lymphoplasmacytic mononuclear cells, have been observed [541]. CNS myelin is normal.

Affected animals are usually responsive to immunosuppressive doses of corticosteroids (e.g., prednisolone at 2 to 4 mg/kg, PO, bid, until clinical remission, followed by the lowest dose that controls the clinical signs [539]. Duration of prednisolone treatment may range from 4 weeks to several months. In one report of steroid-responsive tremor syndrome in 22 dogs, 80% of the dogs responded to immunosuppressive treatment within 3 days [540]. For refractory cases, Parker reported using prednisolone in conjunction with benzodiazepines for maximal therapeutic effect - oral prednisolone (at 1 to 2 mg/kg once a day for 4 weeks; 0.5 to 1 mg/kg once a day for 2 weeks; 0.5 to 1 mg/kg every other day for 2 weeks; and 0.5 to 1 mg/kg every third day for 4 weeks) and oral diazepam (at 0.5 to 1 mg/kg repeated three times a day for 4 weeks; 0.5 to 1 mg/kg repeated twice a day for 4 weeks; and 0.5 to 1 mg/kg once a day for 4 weeks) [538]. Propranolol alone, at 1 mg/kg, PO, tid, improved signs in one dog but was ineffective in another [539]. Prognosis is usually favorable with tremors decreasing in most dogs by the end of the first week of therapy. Some dogs relapse at the end of the treatment, requiring continued medication. Occasionally, relapses may occur after several months or years. Relapses have been reported in some instances within a month of routine vaccination [538]. Anticonvulsant therapy is ineffective in controlling the tremors.

### Tick-borne Encephalitis in Dogs

Tick-borne encephalitis (TBE) is an arboviral infection (member of the family Flaviviridae) of people and occurs as an endemic disease in parts of Asia and in Europe where it is mainly transmitted by the tick *Ixodes ricinus*. The disease has been sporadically reported in dogs in which it causes a fatal encephalitis and tends to have a season occurrence, usually from May to July [555]. A spectrum of clinical signs have been observed in dogs including fever, myoclonus, convulsions, ataxia, hyperesthesia, hemiplegia, tetraparesis, recumbency, opisthotonus, stupor, anisocoria, and nystagmus, lasting from 3 to 7 days. The signs tend to be progressive usually resulting in euthanasia or spontaneous death. Dogs of any age (e.g., 3 months to 10 years) may be affected. CSF studies may reveal mononuclear pleocytosis and TBE antibodies [556]. Neuropathological changes have been similar in affected dogs and include moderate lymphohistiocytic meningitis, widespread neuronal necroses, karyorrhexis of glial cells, numerous neuronophagic nodules, and extensive microgliosis [557]. In the cerebellum, there is loss of Purkinje cells and proliferation of microglial cells in the molecular layer. Numerous perivascular cuffs consisting of lymphocytes, macrophages, plasma cells and, occasionally, red blood cells are seen throughout the brain. The most severe changes are found in the neuropil surrounding the fourth ventricle. Moderate lesions have been seen in the gray matter of the cerebral cortex, hippocampus and molecular and Purkinje cell layers of the cerebellum. While less severe pathology occurs in basal ganglia, thalamus, mesencephalon, nuclei of pons and medulla oblongata. White matter and leptomeninges may show slight perivascular/diffuse lymphocytic infiltration. Spinal cord gray matter (especially ventral horn neurons) may also be severely affected. TBE viral antigen has been detected in the CNS by immunohistologic techniques, although antigen is not detectable in all cases presumably due to rapid virus clearance mechanisms in this disease. The neuropathological changes are very similar to those described in people. In summary, tick-borne encephalitis may be suggested by the seasonal occurrence of a highly febrile, rapidly progressive neurologic disease in dogs originating from TBE endemic regions [555-557]. In one report, serum antibodies to West Nile virus were detected in a dog that also had a high antibody titre to TBE, suggesting this was a cross-reaction between the two closely related flaviviruses [574].

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## **Traumatic Disorders** (6-Feb-2003)

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Central nervous (CNS) system trauma in dogs and cats is commonly encountered in practice. These disorders are among the most devastating of all neurological entities since traumatic injuries often result in death (from initial impact or from euthanasia) or permanent impairment of function. CNS trauma has received more intensive research over the past decade than any other area of human neurology. Considerable advances in knowledge have emanated from this research. We now understand that apart from the primary injury there are important secondary injury processes such as hypoxia, hypotension, mass lesions, increased intracranial pressure, ischemia, free radical production, excitotoxicity, and loss of calcium homeostasis that have a great influence on the clinical outcome. Today, drug research continues to identify therapeutic neuroprotective agents aimed at eliminating or reducing the effects of the cascade of detrimental biochemical and molecular perturbations.

In this chapter, the following topics will be reviewed:

### **Cranial Trauma** **Spinal Trauma**

#### **Cranial Trauma**

Cranial trauma is a relatively common entity in dogs and cats, usually resulting from a fall or an automobile accident, falls, kicks, bites, or penetrating objects (e.g., bullets, knife wounds, porcupine quills, etc) [1-5,114,116,119]. Head trauma may result in different types of primary injury occurring at the time of impact and include skull fractures, scalp lacerations, cortical contusions and lacerations, and intracranial hemorrhage. The extent of the primary brain injury is affected by the degree of the acceleratory/deceleratory and rotational impact forces [6]. In people, such forces may cause tearing of nerve fibers at the moment of impact, called shearing injury or diffuse axonal injury [7], however, Summers and colleagues [8] suggest that this injury has not been confirmed in spontaneous trauma cases in animals. A "coup" contusion occurs in the brain at the site of impact. A "contrecoup" contusion occurs in the area of the brain opposite the point of impact.

As in acute spinal cord trauma, there are important secondary biochemical changes that occur within hours or days after the cranial insult. These events are thought to be associated with progressive hypoxic-ischemic injury of the brain due to multiple factors such as decreased blood flow autoregulation, inadequate cerebral perfusion pressure, altered cerebral metabolism, hemorrhage, increased cytokine and free radical production (e.g., superoxide, hydroxyl, hydrogen peroxide, singlet oxygen, and nitrous oxide), calcium and sodium influx into neurons and glia and endothelial cells along with potassium shift to the extracellular spaces leading to astrocytic swelling and "cytotoxic edema", declining intracellular magnesium levels, elevated levels of excitotoxins (e.g., glutamate and aspartate), and adenosine triphosphatase depletion [9]. The end result of such changes is progressive brain tissue damage and elevated intracranial pressure [6,10,11]. In human trauma patients, mortality is doubled when the deleterious effects of the secondary insults of hypoxia and hypotension are superimposed on severe head injury [9].

Pathological alterations are often heterogeneous and may include intracranial hemorrhage, bone fragments embedded within brain parenchyma, ischemic laminar necrosis of the cerebral cortex, profound hemorrhage into the substance of the brain, especially the midbrain with associated focal or multifocal necrosis of midline structures, and edema. Epidural, subdural, subarachnoid and intraparenchymal hemorrhages may be observed in dogs and cats following head injury [12,116] and bleeding into the inner ear is not infrequent [13]. Subdural hematomas may occur as focal intradural mass lesions or as diffuse lesions over the cerebral cortex, sometimes associated with massive accumulations of blood [12,14]. Subarachnoid hemorrhage is a common consequence of cranial trauma in animals and is usually associated with extensive parenchymal

damage [8]. Hemorrhage into the brain substance (intraparenchymal) from damaged vessels is commonly observed in many forms of cranial injury. This form of bleeding may be short-lived due to vessel spasm and microthrombi formation [15]. Brain hemorrhages may quickly become space-occupying masses (hematomas) that, like brain tumors, compress brain parenchyma, and if unchecked, may lead to widespread brain edema, brain herniation (see below), mid-line shifts, ischemia, brainstem compression and development of deep pontine hemorrhages (Duret hemorrhages) [8,16]. Cerebral edema, either vasogenic from vascular leakage due to openings in the blood-brain barrier (BBB) or cytotoxic, i.e., cell swelling without any loss of the normal impermeability of the BBB (the former is prominent in white matter while the latter affects gray and white matter [17]), can quickly increase intracranial pressure which will reduce cerebral perfusion and further exacerbate cellular hypoxia. Vasogenic edema most commonly occurs with focal injury, brain tumors or abscesses [8,18]. In patients with acute cranial trauma, cytotoxic edema secondary to hypoxia appears to be the dominant form [19]. Recent studies suggest that intracellular swelling of astrocytes is the major form of cytotoxic edema seen in many different kinds of brain injury and one potentially damaging secondary consequence may be an increased release of excitatory amino acids from swollen astrocytes [20]. Since such intracellular swelling is usually not a response to toxins, it has been suggested that the term "cellular edema" is preferable to "cytotoxic edema" [20]. The size of the brain may increase dramatically as a result of cerebral edema, and like hemorrhage (see above) may induce brain herniation. The brain can herniate in several ways in animals [8,21], the four most common being:

- a. the cingulate gyrus herniates under the falx cerebri toward the unaffected hemisphere,
- b. the occipital or temporal lobe (mainly the parahippocampal gyrus) herniates under the tentorium cerebelli (caudal transtentorial herniation),
- c. the rostral cerebellar vermis herniates under the tentorium cerebelli (rostral transtentorial herniation), and
- d. the cerebellum (especially the caudal lobe of the cerebellar vermis) herniates through the foramen magnum.

Myocardial degeneration and necrosis following cranial (and spinal) trauma have been reported in dogs [22]. The myocardial lesions are characterized by subendocardial degeneration of muscle fibers accompanied by mineralization, interstitial edema, and mononuclear infiltration. This neural effect on the myocardium is thought to be mediated via the sympathetic nervous system.

A wide variation of clinical signs commensurate with a multifocal syndrome is usually anticipated in animals with head trauma since lesions may be dispersed at multiple levels of the brain. Some animals may be completely normal after a brief period of unconsciousness lasting a few seconds. Other animals can be:

- a. comatose - unconscious and unresponsive to repeated noxious stimuli;
- b. semicomatose (stuporous) - semiconscious, responsive only to noxious stimuli, demented, with unconscious vocalization;
- c. delirious - disoriented, irritable, fearful, capable of responding to the environment but the response may be inappropriate; or
- d. depressed - lethargic, despondent but capable of responding to the environment in a normal manner.

These disturbances of consciousness are thought to result from lesions involving the ascending reticular activating system within the brainstem. Limbs of recumbent animals may be rigidly extended. Hyperextension of thoracic limbs and neck (opisthotonus) suggests decerebrate rigidity associated with a midbrain lesion. Pupil size may be normal, pinpoint (suggestive of mild or moderate midbrain compression) or dilated and unresponsive to light (suggestive of severe midbrain compression, e.g., from caudal transtentorial herniation). Normal conjugate eye movements (also called oculocephalic reflex, oculovestibular response, or doll's eye movements) may be depressed or absent when the head is rotated (this is suggestive of severe brainstem pathology). Other signs can include blindness, which may be transient (up to 24 hours) or permanent, various cranial nerve deficits (e.g., unilateral ventrolateral strabismus due to oculomotor damage or unilateral medial strabismus due to abducent nerve damage), vestibular and/or cerebellar signs, and abnormal respiration. Several forms of abnormal respiration may be recognized with cranial trauma [23,24]:

- a. Cheyne-Stokes respiration characterized by periods of hyperventilation followed by periods of apnea. This form is often associated with damage to deep cerebral cortical structures, basal ganglia, internal capsule, or diencephalon;
- b. central neurogenic hyperventilation characterized by rapid and regular respiration at a rate of about 25 per minute. This respiratory pattern is due to injury to the pons and lower midbrain, but also occur with cerebral hypoxia/acidosis;
- c. apneustic respiration, characterized by a cyclic pattern of prolonged inspiration followed by expiration and an apneic

- phase. This form is seen with lower brainstem (e.g., medulla oblongata) injury and carries a poor prognosis;
- d. central alveolar hypoventilation characterized by shallow, slow but regular, ventilation most often seen with lesions in the medulla oblongata.

Note that respiratory distress due to non-cardiogenic pulmonary edema also has been reported in animals following cranial trauma [25]. The upper airway may also be compromised as a result of indirect injury to the soft tissues of the neck in animals with blunt trauma to the head [119]. In their report of 2 dogs with respiratory distress following horse kicks to the head, the authors suggested that a kick to the head produces rapid acceleration of the skull, tearing soft tissues of the neck (e.g., hyoid apparatus and larynx), and potential cervical spine fracture/subluxation.

Diagnosis typically is based on historical information relating to the accident, clinical evidence of cranial injury, such as abrasions or penetrating wounds, and/or clinical signs. Skull fractures can be demonstrated using radiography. Of the special imaging techniques, computed tomography may be the preferred modality for evaluating soft tissue changes, hemorrhage and bone [6], although magnetic resonance imaging has been used to visualize the compression and displacement of cerebral tissue and to assess the dynamic changes in cerebral tissue water in experimental subdural bleeding [16]. A recent report suggests that brain parenchymal changes assessed by CT were poor compared to changes seen at necropsy [116]. In addition, meningeal enhancement and mass effect were best visualized with MR. Magnetization transfer imaging is a modality capable of examining the non-water components of brain tissue by examining the effects they have on water protons [26]. It may be used qualitatively to increase the visibility of lesions seen during magnetic resonance angiography and following the administration of an intravenous paramagnetic contrast medium. Quantitatively, it can be used to quantify disease progression in trauma. Collection of cerebrospinal fluid is contraindicated because of the risk of brain herniation.

Treatment of animals with cranial trauma can be medical, surgical, or both. The ABCs of trauma resuscitation must be followed (airway, breathing, cardiovascular status) [6] with correction of hypoxia and hypotension. Dewey [6] recommends maintaining the partial pressure of oxygen ( $\text{PaO}_2$ ) at or above 90 mm Hg for dogs and 100 mm Hg for cats, and that of carbon dioxide ( $\text{PaCO}_2$ ) between 30 and 35 mm Hg, if arterial blood gas analysis is available. He also recommends use of pulse oximeters, nasal or transtracheal oxygen catheters for conscious patients that are not deteriorating, and intubation and ventilation for patients who are losing or have lost consciousness. Hyperventilation as a means of rapidly decreasing intracranial pressure through vasoconstriction of cerebral vessels is no longer recommended as a first line therapy for intracranial hypertension because of the risk of aggravating any pre-existing cerebral ischemia and further compromising cerebral oxygenation [11,27]. Blood pressure should be evaluated very carefully since systemic hypotension is often seen in head trauma patients and it has been considered a primary predictor of outcome in human patients [28] which will lead to decreased cerebral blood flow (especially if autoregulation of blood flow to the brain is impaired), decreased cerebral perfusion pressure, and tissue hypoxia/ischemia. In human trauma patients, vigilant monitoring of both arterial pressure (MABP) and intracranial pressure (ICP) in order to maintain adequate cerebral perfusion pressure (CPP) is a standard practice (by recording both MABP and ICP, the cerebral perfusion pressure can be determined  $\{\text{CPP} = \text{MABP} - \text{ICP}\}$ ) and proven to be beneficial in reducing the incidents of secondary biochemical effects [29,30]. Maintaining CPP at 70 - 80 mm Hg seems to be a critical threshold in humans with cranial trauma. ICP monitoring should also become a standard procedure in animals with head trauma. To date, ICP recordings in animals have been limited [6,31,32]. Normal ICP in dogs and cats lies between 8 and 12 mm Hg [33,34]. Evaluation of ICP using non-invasive transcranial Doppler ultrasonography has recently been reported in dogs [35]. Recently, an implantable solid-state sensor that reliably measures ICP for months has been reported in experimental studies using dogs [36]. The potential clinical application of this sensor and its telemetry includes long-term monitoring of patients with head injury, mass lesions, and hydrocephalus.

Lactated Ringer's solution and 0.9% saline remain the isotonic crystalloid solutions of choice and are administered at a volume of 90 ml/kg/hour in dogs and 60 ml/kg/hour in cats [6,11], to effect. Dewey [6] recommends the colloid hetastarch for restoring normal blood pressure in head injury patients, at a dose of 10 - 20 ml/kg, to effect. It may be given as a rapid bolus in dogs, and in 5 ml/kg increments over 5 to 10 minutes in cats so as to avoid vomiting. Mannitol still remains the primary diuretic to control intracranial pressure [37]. Effective doses range from 0.5 - 1.0 g IV over a 10 - 20 minute period. It may be given as intermittent boluses every 3 - 6 hours [11], but limited to three boluses over a 24-hour period to avoid hypernatremia (See Endogenous Metabolic Disorders) and hyperosmolarity [6]. It has been suggested that concerns about mannitol's "rebound" effect on ICP, its exacerbation of continuing brain hemorrhage, and reverse osmotic shift have been exaggerated [6,11]. Animals should be evaluated approximately every 30 minutes until stable. A response to medical therapy should occur within 4 - 6 hours for a favorable outcome [11]. Corticosteroids and nonglucocorticoid steroid analogs such as the aminosteroid tirilazad mesylate (shown to inhibit lipid peroxidation in experimental studies) have not been shown to be effective in treating head trauma patients and are no longer recommended [6,11,38]. Barbiturates are considered as a rescue therapy in cases of refractory intracranial hypertension, and the use of hypothermia remains to be defined [6,11,39]. New

therapeutic perspectives aimed at controlling biochemical disorders at a cellular level are under active investigation. In one large-scale clinical human trial, pegorgotein, a scavenger of oxygen-derived free radicals, showed no significant reduction in mortality or outcome [40]. Additionally, results of a clinical human trial evaluating CP-101,606 (a postsynaptic antagonist of N-methyl-D-aspartate receptors bearing the NR2B subunit) indicated that CP-101,606 infused for up to 72 hours was well tolerated, penetrated the cerebrospinal fluid (CSF) and brain, and may improve outcome in the brain-injured patient [41].

Surgical management can be considered under the following circumstances:

- a. animals with skull fractures and penetrating wounds,
- b. comatose animals with miotic pupils whose condition has not improved after 24 to 36 hours of medical therapy,
- c. animals whose signs are deteriorating despite aggressive medical treatment,
- d. animals with persistent cerebrospinal fluid leakage.

Various surgical techniques are available for cerebral decompression [6,42,43]. In general, simple linear fractures or elevated fractures of the cranial vault do not require fracture management and are usually associated with less severe brain injury than are fractures of the base of the skull which may damage cranial nerves, result in leakage of cerebrospinal fluid, and may provide a portal for entry of infectious agents and subsequent meningitis. Tension pneumocephalus (e.g., presence of intraventricular air and a fistula between the craniectomy site and ventricular system) is an uncommon but life-threatening complication of craniectomy that requires urgent diagnosis and treatment [118].

Animals presented with seizures or status epilepticus can be treated with Valium using a dose of 5 to 10 mg IV or IM, and repeated as needed every 30 minutes. General supportive treatment includes monitoring of vital signs, maintaining normal body temperature, prevention of decubital ulcers by placing animals on a padded surface with frequent turning, and bladder emptying [44].

Potential complications include cardiac dysrhythmias, coagulopathies, neurogenic pulmonary edema, central diabetes insipidus, aspiration pneumonia from weakened swallowing reflexes, meningitis from open head wounds/skull fractures, and post-trauma epilepsy, usually within 2 years of head trauma [6,11]. Secondary hypoadrenocorticism associated with head trauma has been reported in a dog [45]. Panhypopituitarism was not confirmed. The hypoadrenocorticism was successfully treated with prednisone.

Prognosis is guarded. Some animals are normal after a brief period of unconsciousness. Others may have a stable condition for several days before showing signs of deterioration. Stuporous or comatose animals with dilated unresponsive pupils have a poor prognosis. A period of coma lasting 48 hours or longer is a grave prognostic sign. Deteriorating clinical signs such as depression progressing to coma, or normal or miotic pupils becoming dilated and unresponsive are ominous and indicative of progressive brain swelling or transtentorial herniation. It has been recently reported that CT findings in dogs and cats with head trauma are unreliable for determining prognosis [116]. A modified Glasgow Coma Scale (MGCS) (see Table 1) (i.e., modified from one used in people) has been proposed as an aid to assess prognosis in animals with cranial trauma [1]. Each category (level of consciousness, motor activity, brainstem reflex) receives a score of 1 to 6. A total score of 3 to 8, without sign of improvement, indicates a grave prognosis; 9 to 14, a poor to guarded prognosis; and 15 to 18, a good prognosis. In a recent study of 38 dogs, the MGCS predicted the probability of survival in the first 48 hours after head trauma in an almost linear fashion, with a 50% probability of survival in a patient with a score of 8 (Fig. 1) [46]. Gender, weight, age and presence of skull fractures did not predict survival. As the authors of this report stated, this study did not take into account any deaths after 48 hours and insufficient data were available for long-term follow-up. In human medicine, the Glasgow Coma Scale has been the most reliable indicator of the severity of injury and deterioration or improvement, and the initial score often influences early treatment [9].

**Table 1. Modified Glasgow Coma Scale (MGCS) for Dogs and Cats**

Category	Grade
<b>Motor activity</b>	
Normal gait, normal spinal reflexes	6

Category	Grade
Hemiparesis, tetraparesis	5
Recumbent, intermittent extensor rigidity	4
Recumbent, constant extensor rigidity	3
Recumbent, constant extensor rigidity, opisthotonus	2
Recumbent, depressed/absent spinal reflexes and muscle tone	1
<b>Brain stem reflexes</b>	
Normal pupillary reflexes, with normal oculoccephalic reflexes	6
Slow pupillary reflexes, with normal to depressed oculoccephalic reflexes	5
Bilateral miosis, with normal to depressed oculoccephalic reflexes	4
Pinpoint pupils, with depressed to absent oculoccephalic reflexes	3
Unilateral, unresponsive mydriasis, with depressed to absent oculoccephalic reflexes	2
Bilateral, unresponsive mydriasis, with depressed to absent oculoccephalic reflexes	1
<b>Level of consciousness</b>	
Occasional period of alertness and responsive to environment	6
Depression/delirium, capable of responding to environment but response inappropriate	5
Semicomatose, responsive to visual stimuli	4
Semicomatose, responsive to auditory stimuli	3
Semicomatose, responsive only to repeated noxious stimuli	2
Comatose, unresponsive to repeated noxious stimuli	1
<b>Total score (sum of the three categories)</b>	
Grave prognosis	3 - 8
Poor to guarded prognosis	9 - 14
Good prognosis	15 - 18

Courtesy of Dr. A Shores.

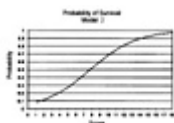


Figure 1. Graph of the probability of survival of a head trauma patient as it relates to the modified Glasgow Coma Scale score assigned to the patient upon admission. (Reprinted with permission from: Platt SR, Radaelli ST, McDonnell JJ. The prognostic value of the modified Glasgow Coma Scale in head trauma in dogs. J Vet Intern Med 2001;15:581-584.) - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

It should be noted that in the acute stage of severe head injury in humans, hyperglycemia (e.g., 200 - 250 mg/dl) and

elevation of serum levels of catecholamines (epinephrine, norepinephrine, and dopamine) are common components of the systemic stress response, significant indicators of severity, and significant predictors of outcome [47-49]. Another metabolic marker associated with poor outcome in children with acute head injuries is hypokalemia [50]. These markers are often seen in patients with lower Glasgow Coma scores. Results of recent clinical studies in dogs and cats with acute spontaneous head trauma indicated that blood glucose concentration was also significantly higher in animals with head trauma than in the controls [51]. While blood glucose concentration was significantly associated with severity of head trauma, it was not associated with outcome. Since hyperglycemia has been shown in both experimental and clinical studies to exacerbate the severity of brain injury during ischemic/hypoxic conditions [52-55] (possibly due to lactic acidosis), efforts are made to prevent it by carefully regulating the glucose and insulin intake in the nutritional management of human patients with head injury [56]. Routine neuroimaging studies are recommended for all animals with head injury, regardless of severity [115]. In this study, dogs with a MGSC score of 15 - 18, and thus graded as having "mild" head trauma and a good prognosis were shown to have myriad abnormalities using computed tomography, including skull fractures, parenchymal damage, hydrocephalus (unilateral and bilateral), hemorrhage, and mass effect.

### **Spinal Trauma**

Spinal trauma of sufficient magnitude to cause vertebral fractures, luxations/subluxations, traumatic disk extrusion, or dural tearing usually results in spinal cord concussion, laceration, compression or distraction [57]. The severity of injury depends on the velocity, degree, and duration of the compressive/distractive force. Spinal injury of this type is one of the more frequent neurological disorders seen in clinical practice. Common causes include automobile accidents, falls, gunshot wounds, and fight injuries. Accidental penetrating injuries of the vertebral canal are extremely uncommon, however, acute onset tetraparesis as a sequela to an oropharyngeal stick injury has been reported in a dog [120]. Fractures and luxations of the spine generally occur at the junction of movable and stable vertebral segments, such as atlanto-occipital, cervicothoracic, thoracolumbar, and lumbosacral areas. In one review of spinal trauma in 41 dogs, the majority of vertebral fractures were in the lumbar region while most vertebral luxations occurred at the thoracolumbar junction [58]. Cervical spinal subluxation at the C5-C6 level has been reported in several dogs as a result of fight injuries, suggesting a possible anatomical predisposition for this type of injury [59]. The axis may be more commonly fractured than other cervical vertebrae. External traumatic injuries of the spinal column have been arbitrarily divided into (a) ventral compartment injuries involving the vertebral body, intervertebral disk, dorsal/ventral longitudinal ligaments, and intertransverse ligaments and (b) dorsal compartment injuries involving the lamina, pedicles, dorsal spinal processes, articular processes, and various ligaments, e.g., supraspinous, interspinous, and interarcuate [60]. Combined compartment injuries are often seen in animals following spinal trauma. A three-compartment model has also been proposed [61]: the dorsal compartment consists of the articular facets, pedicles, laminae, spinous processes, and the ligamentum flavum; the middle compartment contains the dorsal longitudinal ligament, the dorsal annulus, and the dorsal vertebral body; and the ventral compartment consists of the remainder of the vertebral body, the lateral and ventral portions of the annulus, and the ventral longitudinal ligament. When two or three of the compartments are damaged, the spine is considerably unstable. The spine is relatively stable if only one of the compartments is damaged, although in a recent spinal biomechanical study it was suggested that thoracolumbar spinal fractures involving only the vertebral body might significantly destabilize the spine [62].

Apart from the external causes of spinal cord trauma, acute injury can arise from internal factors including intervertebral disk disease [63] and congenital deformities such as atlantoaxial subluxation. Spontaneous spinal fractures attributable to severe osteopenia and hypocalcaemia have been recently reported in cats with nutritional secondary hyperparathyroidism (See Nutritional Disorders) [64], while a dorsally displaced Salter-Harris type I fracture of the cranial portion of the fourth cervical vertebra with the endplate present in the vertebral canal has been described in an adult dog with congenital hypothyroidism [65].

Neurological deficits that follow acute traumatic spinal cord injury result from direct (primary injury) mechanical disruption of neuronal pathways instantly after the traumatic event, as well as from delayed tissue injury (secondary injury) that develops over a period of hours to days after the primary insult. This delayed injury relates to a physiological cascade of events that begins shortly after the injury and includes ischemia, hypoxia, edema and various biochemical events that are harmful to the spinal cord [9]. The degree of ischemia is positively correlated with the severity of the injury and is progressive [66]. In association with reduction of spinal cord blood flow [67,68] there are several metabolic changes that occur almost immediately after spinal cord injury [69-72]. They include electrolyte disturbances such as decreased intracellular free magnesium concentration, increased intracellular calcium level, increased extracellular potassium level, and increased sodium permeability. Additionally, there is loss of high-energy phosphates, lactic acidosis, decline in intracellular pH, reduced oxygen tension, and inflammation and neuronophagia by polymorphonuclear leukocytes. There is now much evidence that the decline in spinal cord blood flow may involve release or activation of endogenous autodestructive factors,

including free radicals, lipid peroxidation, monoamines, free fatty acids, arachidonic acid metabolites (prostaglandins, leukotrienes, and thromboxanes), excitatory neurotransmitter accumulation (e.g., glutamate and aspartate), and endogenous opiate activation [9,73-75]. The collective result of these events is ischemia, edema, membrane destruction, cell death, and eventually, serious if not permanent neurological dysfunction [9].

Pathological findings include petechial hemorrhages progressing to hemorrhagic necrosis over a 24-hour period [76]. These changes are most severe in the gray matter of the spinal cord, with subsequent spread to the white matter. The gray matter vulnerability [77] may be due to several factors [76]:

- a. in contrast to the slightly packed fiber tracts of the white matter, the neuropil of the gray matter is easily separated by fluid or blood,
- b. because of the inelastic pial membrane, any increase in intramedullary pressure (secondary to hemorrhage/edema) is concentrated centrally, or
- c. injured tissues have supranormal metabolic demands, and although gray matter/white matter blood flow ratio is 5:1, the gray matter metabolic needs may exceed the available blood flow.

In contrast, slowly, progressive spinal cord compression, as seen in the Wobbler syndrome or cervical spondylomyelopathy, in dogs with Hansen type 2 disk protrusion, or in dogs and cats with extramedullary masses, tends to be characterized by loss of axons and their myelin sheaths in all funiculi leading to a fibrous astrogliosis and eventually focal spinal cord atrophy [57]. There is no acute hemorrhage or necrosis as seen in acute spinal cord injury, although a reduction of ventral motor neurons in the cervical gray matter may occur from intermittent ischemia. Extensive partial demyelination was found in an experimental model of chronic spinal cord compression in kittens [78].

Animals with acute spinal cord injury should be handled carefully with minimal manipulation so as to avoid further cord injury from any unstable vertebrae. Traumatized animals should be placed in lateral recumbency upon admission and maintained in this posture during clinical/neurological examination and radiographic procedures. Struggling animals can be restrained and immobilized by being firmly taped to a rigid backboard [79]. Animals should be immediately evaluated for airway obstruction, shock, visible hemorrhage or limb fractures. Clinical signs typically are acute in onset, usually nonprogressive, and either stable or improve with time. In rare cases in which clinical signs are progressive, continued bleeding and/or excessive bony movement at the site of injury should be suspected. Clinical syndromes seen with spinal fractures and luxations are cervical, cervicothoracic, thoracolumbar or lumbosacral [80]. Localization of the lesion in such cases usually can be determined with the animal in lateral recumbency.

Radiography usually will demonstrate obvious fractures and luxations of the vertebral column [81]. The degree of luxation has no prognostic value since the luxation that is seen radiographically may have been much worse at the time of the injury. For example, a severe luxation resulting in spinal cord transection may return to normal immediately after the accident. Traumatic disk extrusion sometimes occurs with spinal injury and may be suggested radiographically by the presence of a narrowed disk space. Severe spinal cord contusion can occur in the absence of vertebral or diskal damage. In such cases, myelographic studies may help to delineate an area of spinal cord swelling which may be present up to 36 hours after the injury. Myelography may also delineate any tears in the dura mater [82]. The entire vertebral column should be evaluated radiographically to rule out more than one site of vertebral fracture, luxation or traumatic disk extrusion. Diagnosis of cervical spinal luxation using three-dimensional CT reconstruction has been reported [83]. MRI scans in spinal trauma patients can reveal focal edema within the spinal cord in absence of extraparenchymal compression [84]. Spinal cord and peripheral nerve evoked potentials may be sensitive indicators of severity and location of acute spinal cord compression [77,85,86]. Dogs with neck and back pain caused by acute and chronic spinal cord compression have significantly more oxytocin in their CSF than clinically normal dogs [87]. CSF levels of eicosanoids (prostaglandins, leukotrienes, and thromboxanes) are also increased in dogs during the first 7 days following acute spinal trauma [74]. In this study, there was a good correlation between CSF leukotriene C4 levels and the neurological severity.

Prompt medical treatment is mandatory. Methylprednisolone succinate (MPS) presently remains the drug of choice in people with acute spinal cord injury due to its neuroprotective effects against the physiological cascade associated with the secondary spinal injury events [88-92]. These beneficial effects occur when MPS is given within 8 hours of injury. Clinical studies in humans suggest that spinal cord damage may be exacerbated if MPS treatment is initiated more than 8 hours after injury [93,94]. The recommended dose of MPS in human patients is 30 mg/kg as a bolus administered over 15 minutes followed by an intravenous infusion of 5.4 mg/kg/hour for 24 hours (in patients who receive the bolus within 3 hours of

injury) or for 48 hours (in patients who received the bolus 3 - 8 hours post injury). A similar regimen for MPS (i.e., IV bolus of 30 mg/kg followed by 5.4 mg/kg/hour for 24 hours) [95] has been proposed for spinal cord injury in dogs. Bagley suggests an empirical modification [96]: an initial bolus of 30 mg/kg IV followed by additional doses of 15 mg/kg IV of MPS given at 2 and 6 hours after the initial dose. Surprisingly, results of controlled clinical trials using the human MPS regimen have yet to be reported in dogs and it still remains uncertain whether the use of MPS is actually helpful in dogs with spinal cord injury [73]. In one experimental canine model of spinal trauma, MPS had no clinical efficacy [97]. In cats, the recommended regimen for MPS is 30 mg/kg as an initial intravenous bolus, followed by 15 mg/kg at 2 and 6 hours, and continues with an intravenous infusion of 2.5 mg/kg/hour for 42 hours (see review by Olby [73]). The use of dexamethasone for treating animals with acute spinal cord trauma is no longer recommended due to doubts about its efficacy and because of its detrimental side effects [23,73]. Other potential neuroprotective drugs such as thyrotropin-releasing hormone, the 21-aminosteroids, kappa opioid agonists, and GM1 gangliosides have been reviewed and await clinical trials [43,73,98,99], although the 21-aminosteroids (drugs which are similar in structure to MPS but without the glucocorticoid receptor-mediated effects) have been shown to be beneficial in experimental spinal trauma studies in cats [100-103] but not in dogs [97]. Potential complications of glucocorticosteroids include vomiting, hypotension, immunosuppression, gastrointestinal hemorrhage, ulceration, colonic perforation, and pancreatitis [73,79,104,105]. Prophylactic use of intestinal protectants, such as bismuth subsalicylate (i.e., Pepto-Bismol) in conjunction with frequent administration (at least four times daily) of either antacids (such as magnesium or aluminum hydroxide) or H<sub>2</sub> antagonists, such as cimetidine (i.e., Tagamet, 20 mg/kg, PO, tid) also may reduce the prevalence of gastrointestinal hemorrhage. Corticosteroids should be stopped immediately, when gastrointestinal complications are noted.

In patients with fractures and luxations, medical management is usually combined with prompt surgical intervention such as decompression of the spinal cord, vertebral reduction, and internal stabilization (e.g., use of Steinman pins and polymethylmethacrylate or coated polypropylene) [42,96,106,107,117]. The choice of stabilization technique is contingent on the location in the spinal column, size of the patient, and the surgeon's experience [106,117]. Acute surgical intervention is also required in cases with neurological deterioration associated with spinal cord compression from bone and disk fragments, hematoma, or unreduced subluxation [9]. Experimental studies indicate that surgical intervention should occur as early as possible, e.g., within an hour following compressive spinal cord injury [108]. In this report, there was no neurological recovery in dogs when compression lasted six hours or more. Durotomy or myelotomy have been recommended in animals with spinal cord swelling but without extradural compression [11]. Animals with luxations and mild paresis may require only internal stabilization without decompression. All animals undergoing surgery also should be confined for 2 to 3 weeks after surgery. Paretic animals without evidence of vertebral column injury can be managed with strict cage confinement for 4 to 6 weeks [79]. Additionally, external support bandages or casts applied for 4 to 6 weeks may be used as forms of non-surgical treatment [61,79,96,107]. Decompressive surgery and removal of a foreign body 3 days after injury was successful in a dog with acute spinal cord compression secondary to an oropharyngeal stick injury [120].

Recent studies indicate that an applied electric field (oscillating electric field stimulation, approximately 500 to 600  $\mu\text{V}/\text{mm}$ ) in which the polarity is reversed every 15 minutes can improve the outcome from naturally occurring severe, acute spinal cord injury in dogs [109]. The oscillating extracellular voltage gradient reduces the density and influences the orientation of astrocytes in injured spinal cord, which form a major component of the scar that forms in response to injury [110].

Prognosis of animals with acute spinal trauma is always guarded and is influenced by several factors, including the degree and location of spinal cord damage and stability of the fixation technique [104,106,117]. Spinal cord dysfunction reflects varying degrees of damage to the gray matter, white matter, or both. With cranial cervical and thoracolumbar cord injuries, clinical signs primarily reflect damage to ascending and descending tracts of the white matter. More heavily myelinated fibers show earliest dysfunction; thus, signs of progressive neurological deterioration in order of presentation are [2]:

- a. loss of proprioception,
- b. motor dysfunction such as paresis and paralysis, and
- c. sensory disturbances including hypesthesia, hyperesthesia, and anesthesia.

Neurological recovery occurs in reverse order; however, proprioceptive loss may be permanent. In cranial cervical and thoracolumbar spinal cord regions, severe gray matter lesions have little clinical significance, since no major muscle groups or vital organs will be deprived of innervation. In contrast, gray matter lesions in caudal lumbar segments involve the lumbosacral intumescence, which provides innervation to the pelvic limb muscles and bladder. An extensive gray matter lesion in this region carries a very poor prognosis. Similarly, severe gray matter lesions in caudal cervical segments may result in death from respiratory failure due to damage to neurons giving rise to the phrenic nerves. Also, gray matter damage in cervicothoracic cord segments (the cervical intumescence) will carry a guarded prognosis because of denervation of thoracic limb muscles. In animals with disk disease, the degree and rate of clinical recovery are largely based upon the rate of disk extrusion. Gradual cord compression over several hours has a much more favorable prognosis than compression



occurring within seconds or minutes. The prognosis in many cervical injuries may be better than that in other spinal regions since the ratio of canal to cord diameter is greatest in the cervical region, and therefore a greater vertebral displacement can be tolerated [2]. Animals with gunshot wounds involving the spine have a very guarded prognosis [5]. One prognostic indicator of spinal cord injury is the vocal response to a noxious stimulus that is easily tested by applying digital pressure to the nail bed. Absence of deep pain perception (nociception) is an indication that a severe spinal cord injury has occurred. In general, animals that are paretic or paralyzed, but have normal sensation to a painful stimulus, have a favorable prognosis following medical and/or surgical treatment. Clinical signs can be expected to improve within 2 to 3 weeks. Animals that are paralyzed, with loss of bladder control and reduced sensation to a noxious stimulus, have a guarded to favorable prognosis following surgical decompression. Any clinical improvement should be seen within 3 to 6 weeks. Paralyzed animals with loss of bladder control and loss of sensation to painful stimuli for greater than 24 - 48 hours have a guarded to poor prognosis [11,96,111]. Prognosis is considered hopeless if sensation to a noxious stimulus is absent in an animal with 100% or greater displacement of the vertebral canal [96]. A functional scoring system for evaluating pelvic limb gait in dogs recovering from acute spinal cord injuries associated with disk protrusions has been developed [112]. This methodology examines the rate and level of functional recovery and may be useful in clinical drug trials aimed at improving the outcome of acute spinal cord injuries.

Nursing care of paraplegic or tetraplegic animals is important to prevent decubital ulcers, urinary tract infections, and disuse muscle atrophy [104]. Many successful surgical procedures have been jeopardized by inadequate supportive care. Adequate alimentation during convalescence is extremely important in short- and long-term therapy. Oral or intravenous fluid therapy should be adequate to correct or prevent dehydration. Paralyzed animals need to be maintained in a sanitary environment, with frequent removal of soiled bedding. Multiple sponge baths are given daily when the animal is frequently soiled with urine or feces. Petroleum jelly applied to the preputial or vulval areas can be used for waterproofing and averting urine scalds. Decubital ulcers can be prevented or delayed by use of waterbeds, air mattresses, or foam rubber pads. Alternating right and left lateral recumbency, at least four times daily, is recommended for paralyzed animals. Post-operative pain can be reduced using opiate analgesics, e.g., morphine, 0.3 mg/kg IM, every 4 hours for the first 12 hours in conjunction with a dermal patch (e.g., Duragesic, Fentanyl Transdermal system) [96].

Active physiotherapy (see rehabilitation in chapter IV) to delay muscle atrophy from disuse is an integral part of the nursing care of paralyzed animals. Through the use of slings, animals should be encouraged to support themselves. Such "standing" exercises can be performed for 10 minutes, 5 or 6 times daily. Additional exercises include supervised swimming for 15 to 20 minutes twice daily, vigorous muscle massaging, and passive manipulation of limbs. Muscle stimulators, used in human physical therapy, actively stimulate muscles to effect active flexion and extension of the limbs. Animals need to be encouraged to stand and walk, initially with assistance, and then unassisted. After an animal has been in the hospital for 1 to 2 weeks, owners should continue physiotherapy at home. Some animals may respond faster in familiar surroundings than in the hospital. Bladder management is of paramount importance in the paralyzed patient. Since most animals lose control of micturition, urine evacuation from the bladder is incomplete and this predisposes the animal to urinary tract infection and bladder overdistension, with subsequent bladder atony. Catheterization, the most effective method for emptying the bladder, should be performed three times a day using soft, sterilized rubber catheters. Indwelling catheters frequently lead to urinary tract infections. However, in female patients, human urinary drainage systems consisting of a Foley catheter and sterile closed system drainage bags are an excellent method of maintaining bladder decompression. It is good practice to instill prophylactic antibiotic solutions, such as nitrofurazone or neomycin, into the bladder following removal of urine. In the event that urinary tract infection occurs, urine should be cultured, and appropriate systemic or intraurinary antibiotic therapy initiated. Manual bladder expression may be possible in some animals, especially females (note: in animals with a lumbosacral syndrome, the bladder is flaccid and easy to evacuate manually). Care should be taken since overzealous manipulation can traumatize the bladder. Contractile function in animals with an upper motor neuron bladder (i.e., with lesions between T3 and L3) may return in several weeks as a sacral reflex ("reflex bladder") but voiding tends to be involuntary, incomplete, and poorly coordinated (detrusor-urethral dyssynergia) [113]. In dogs with resistance to evacuation of the bladder by catheterization or manual expression, the alpha blocker phenoxybenzamine (0.25 - 0.5 mg/kg, PO, sid or bid, in dogs; or 1.25 - 7.5 mg/cat, PO, sid or bid) or a skeletal muscle relaxant, such as diazepam (2 - 10 mg/dog PO, tid; or 1.0 - 2.5 mg/cat, PO, tid or 0.5 mg/kg, IV) may reduce urethral tone [113].

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## Epilepsy (13-Jul-2004)

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### Introduction

Epilepsy is one of the most common neurological disorders in canines and felines. Epilepsy is an episodic illness caused by repeated excessive and hypersynchronous abnormal electrical activity of neurons in the brain. Epilepsy is more than convulsions. A broad variety of clinical phenomena may reflect epileptic seizure activity e.g., behavioural or gastrointestinal signs. Therefore, the recognition of epilepsy implies knowledge of the phenomenology representing different types of seizures. Observations of suspected seizure activity, seizure symptomatology reported by the owner and video documentation of seizures are essential when trying to establish a diagnosis of epilepsy. Electroencephalography, brain imaging and cerebrospinal fluid (CSF) examination among others, may disclose underlying pathological processes causing epilepsy. Animals with epilepsy are time consuming patients. A continued evaluation of the owners' compliance with given instructions concerning actual seizure frequency, antiepileptic treatment, measurement of antiepileptic drug levels, monitoring of potential adverse effects and additional owner counseling is required to manage these patients successfully.

#### History

#### Definition of Epilepsy

#### Epidemiology

#### Pathophysiology

#### Genetics

#### Classification of Epilepsy and Epileptic Seizures

#### Classification of Epilepsy

#### Classification of Epileptic Seizures

- Primary Generalized Seizures
- Partial Seizures
  - Simple and Complex Partial Seizures
  - Partial Seizures with Secondary Generalization
    - Clinical Signs in Partial Seizures
    - Prodromes
    - Postictal Signs
    - Classification - Future Perspectives

#### Diagnostic Evaluation

- Differential Diagnosis
- Diagnostic Work-up

#### Long-term Therapy of Epilepsy

- General Therapeutic Considerations
- Antiepileptic Drugs
- Complications Associated with Long-term
  - Phenobarbital (Primidone) and Potassium
  - Bromide Treatment
- Therapeutic Failure
- Withdrawal of Antiepileptic Drugs
- Instructions to Owners

#### Non-medical Treatment for Epilepsy

- Epilepsy Surgery
- Vagal Nerve Stimulation
- Ketogenic Diet

#### Status Epilepticus (SE)

- Classification of SE
- Convulsive SE
- The Pathophysiology of Convulsive SE
- Management of Convulsive SE
- Anticonvulsive Drugs in SE
- Therapeutic Failure in SE
- Instructions to Owners

#### Closing Remarks

### History

The word epilepsy originates from the Greek word epilepsia meaning to be taken, seized or attacked. This condition has been recognized in Man since antiquity. The Greek physician and philosopher Hippocrates (460 - 377 B.C.) believed that the cause of epileptic seizures should be found in the brain. The Greek physician Galén (130 - 210 A.D.) viewed epileptic seizures as a symptom of intracranial dysfunction or systemic disease, caused by an accumulation of mucous in the arterial system. During the Middle Ages epilepsy was thought to be associated with supernatural forces, because of the vigorous symptomatology, especially of convulsions. Humans suffering from epilepsy have been thought to be insane, or possessed by demons in the 16th and 17th centuries. As a consequence, treatment of epilepsy included exorcism and bloodletting, and a variety of substances e.g., brew of mistletoe, blood from a decapitated man and a pulverized cranium were given to aid the

sick person.

In the 19th century the gap between ignorance and understanding of epilepsy began to close. The physician Calmeil in 1824 made the first attempt to classify epileptic seizures according to their symptomatology. The neurologist John Hughlings Jackson proposed that a classification of epilepsy should be based upon anatomical localization, physiological imbalance and the pathological process [1]. He made a distinction between partial and generalized seizures based upon clinical observations. Electroencephalography (EEG), introduced in 1929 by the German psychiatrist Hans Berger, added immensely to the understanding of epileptogenesis [2].

The influence of human epileptology in veterinary medicine is hard to overlook. Much of what is reported on epilepsy in animals is based upon the study of seizures in Man. An early paper of canine epilepsy is found in "Archiv für Wissenschaftliche und Praktische Tierheilkunde" [3]. The authors compare the symptomatology of epileptic seizures in Man and dog. The textbook "Die Nervekrankheiten unsere Hunde" [4] uses the terms genuine, essential or idiopathic epilepsy and symptomatic epilepsy as they were used in human epilepsy terminology at that time. In veterinary medicine - EEG was introduced as a laboratory test in the early sixties [5-7]. Terrell A Holliday has contributed greatly to the understanding of canine epilepsy by introducing and refining this investigation in veterinary epileptology [8-10]. However, EEG has never become a routine investigation in the diagnostic management of canine and feline epilepsy patients. Only a limited number of studies have been published on this subject [11-15].

### **Definition of Epilepsy**

Epilepsy is defined as a condition characterized by recurrent seizures (two or more) - a clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurons in the brain. The clinical manifestation consists of a sudden and transitory abnormal phenomenon which may include alterations of consciousness, motor, sensory, autonomic or psychic events, perceived by the patient or an observer [16]. Thus, epileptic seizures are a sign of cerebral dysfunction. Three main characteristics of epileptic seizures are: the loss of control (in various degrees), the episodic (paroxysmic) nature of the attacks (they start suddenly and they terminate suddenly), and the repetitive clinical pattern (attacks are identical from episode to episode).

### **Epidemiology**

Epilepsy is the most common neurological disorder in canines. The prevalence of epilepsy in the canine population has been estimated to vary from 0.5% to 5.0% [17-20]. In cats the prevalence of epilepsy has been estimated at 0.5% [20].

No studies exist in a randomly selected cohort, however, of the lifetime prevalence in the general canine or feline population. Investigations of canine epilepsy are often carried out in hospital-referral based or otherwise pre-selected populations [13,21-23]. This is of no concern as long as descriptive studies are performed, i.e., studies focusing on description of seizures, treatment and prognosis of the population investigated [24]. However, when investigating the prevalence and clinical pattern (distribution of seizure types) of epilepsy, a study based upon random sampling is crucial in order to avoid selection bias. A prospective two-phase cross-sectional study of epilepsy, reporting a prevalence of 3.1%, has been conducted in Danish pedigree Labrador Retrievers, a reference population constituting 29,602 individuals [25].

A slight predilection for epilepsy in males has been documented in several studies [18,25-29]. The distribution of idiopathic epilepsy and symptomatic epilepsy has been reported to be 44% and 46% respectively in 50 dogs in an American study (10% experienced non-epileptic seizures) [28]. A Danish study reported a distribution of idiopathic epilepsy, symptomatic epilepsy and cryptogenic epilepsy of 25%, 16% and 45% respectively in a population of 63 dogs (14% could not be classified) [29]. Environmental conditions may provoke seizures in humans and animals suffering from epilepsy. Flashing lights, high sounds, sleep deprivation, stress etc., are known triggers of seizure activity in susceptible individuals.

No relationship between seasons, holidays, days of the week or astrology and seizure frequency has been demonstrated in dogs [23,27,28].

Epilepsy is not necessarily a life long condition. Epilepsy has the potential to be self-limiting. In humans, epilepsy is now regarded as a condition that, for the majority of patients will remit spontaneously or by drug induction [30,31]. The results of a study on Labrador Retrievers suggest that remission of epilepsy also occurs in dogs [25]. In a hospital based population, 30 - 40% of epileptic animals have been reported to achieve seizure freedom on antiepileptic treatment. Seizure reduction was obtained in about 50% [20]. In a study of 30 cats with seizure disorders outcome was documented on the basis of survival and seizure frequency at follow-up (3 - 21 month). In this study 17 cats had a good outcome: eleven seizure free and 6 with a low seizure frequency [32].

Epidemiological research on epilepsy is an excellent tool for studying the characteristics of epilepsy. It provides important information on the natural history of the condition, and thus is useful in the diagnostic and prognostic work with epileptic patients.

The lack of standardized definitions or a defined methodology especially with regard to patient selection bias, diagnostic accuracy and seizure classification in the veterinary literature makes it difficult to compare results among studies. Different investigators have not used the same definitions of epilepsy and epileptic seizures, along with different case ascertainment methods and classification models, a phenomenon also known from epidemiological studies of epilepsy in humans [16,33,34].

### **Pathophysiology**

The susceptibility for generating an epileptic seizure varies between individuals. Some may have a lower threshold for epileptic seizures and are therefore more likely to develop this condition. If provoked sufficiently any brain can elicit a seizure. Therefore, an animal may experience a single seizure as a sign of transient cerebral overload. Only if seizures become recurrent and are not provoked by systemic disease, is the animal diagnosed with epilepsy.

Seizure phenomenology varies from patient to patient and more than one seizure type can occur within the same patient. No relationship exists between the clinical signs expressed and the underlying etiology.

Irrespective of the fact that epilepsy can be caused by a variety of intracranial structural, cellular or molecular conditions and manifests itself in different ways, the epileptic seizure always reflect abnormal hypersynchronous electrical activity of neurons, caused by an imbalance between excitation and inhibition in the brain. The main representative of excitation in the brain is the excitatory postsynaptic potential (EPSP) whereas that of inhibition is the inhibitory postsynaptic potential (IPSP) [35]. The neuronal membrane potential is regulated by an accurate balance between EPSPs and IPSPs. If this balance is compromised, an epileptic seizure can be generated.

More than 100 neurotransmitters or neuromodulators have been shown to play a role in the process of neuronal excitation. Excitatory amino acids, especially L-glutamate, act at more than half the neuronal synapses in the brain, hereby playing a major role in the spread of seizure activity [36]. There is an increased release of glutamate in the brain associated with epileptic activity.

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter of the CNS. GABAergic inhibition can be pre-synaptic (release of GABA from the GABAergic nerve terminal into presynaptic nerve terminals causing a reduction of neuro-transmitter release) or postsynaptic (caused by the interaction of GABA with specific postsynaptic receptors). GABA released from GABAergic nerve terminals binds to two distinct types of GABA receptors GABA-A and GABA-B receptors to produce neuronal inhibition [37] GABA is catabolized postsynaptically by GABA-transaminase. Dysfunction of the GABA-system can be caused by defects of synaptic GABA release, or of the postsynaptic GABA receptor. Low GABA and high glutamate values have been demonstrated in the cerebrospinal fluid of epileptic dogs [38].

Under normal conditions the excitatory post-synaptic potentials are followed immediately by GABAergic inhibition. Neuronal hypersynchronization occurs if excitatory mechanisms dominate, either initiated by increased excitation or decreased inhibition. As the abnormal neuronal hypersynchronous activity continues, more and more neurons will be activated (high frequency depolarization/repolarization), generating the epileptic seizure. The abnormal hypersynchronization gives rise to the characteristic abnormalities that can be registered in the electroencephalogram. The physiologic basis of neuronal excitability has been reviewed in detail by March [39]. The existence of excitatory connections between pyramidal neurons generating epileptic bursts through a positive-feedback mechanism in epileptogenic areas and the fact that neurons in some epilepsy prone regions, (e.g. the structures of the limbic system in the temporal lobe, especially the hippocampal CA3 region), possess the capability to generate "intrinsic bursts", dependent on voltage dependent calcium currents or persistent sodium currents has been identified as key features of epileptogenic circuits [174].

Sex hormones influence the regulation of GABAergic transmission in the CNS. Animal models have shown that the infusion of estrogens, lower the threshold for experimentally provoked seizures, and that this effect of estrogen is intensified if a cortical lesion is already present. Progesterone has been shown to possess an inhibitory effect on spontaneous and experimentally provoked seizures [40,41]. Progesterone probably works through a direct activation of the GABA complex to enhance the effect of GABA. Additionally, progesterone possesses the capability of inhibiting glutamatergic activity. The convulsant/anticonvulsant effects of estrogens and progesterones, respectively, are demonstrated in women with catamenial epilepsy (seizure clustering around the time of menses). There is an increase in seizure frequency, immediately preceding the menstrual period, which correlates to a decrease in progesterone level, and an additional increase in seizure frequency immediately preceding the time of ovulation, correlating with a high estrogen level with no simultaneous increase in progesterone. At the end of ovulation, simultaneously with an increase in the progesterone level, the seizure frequency decreases [42,43]. The relationship between sex hormones and epileptic seizures has not been investigated in natural occurring epilepsy in dogs and cats, but these mechanisms might exist in bitches/mares experiencing clusters of seizures associated with hormonal fluctuations.



## Genetics

Epilepsy can occur in any canine and feline breed as well as in mixed breeds. A familial predisposition for epilepsy in dogs has been reported for many breeds, e.g., Beagle, Keeshound, Belgian Tervueren, Golden Retriever, Labrador Retriever, Vizsla and Shetland sheepdog [15,18,21,22,25,26,44-46,163,164]. The hypothesis of a polygenic, recessive mode of inheritance has been suggested in the Bernese mountain dog and in Labrador Retrievers [21,47]. It has been suggested that a single locus with a large effect on the incidence of seizures may be segregation in the Belgian Tervueren dog [48]. In Vizslas an autosomal recessive trait has been suggested [164].

## Classification of Epilepsy and Epileptic Seizures

Do We Need Classification? - "The Diagnosis of epilepsy is essentially clinical, based on a bonafide history of epileptic seizures. The clinical manifestation consists of a sudden and transitory abnormal phenomenon which may include alterations of consciousness, motor, sensory, autonomic or psychic events, perceived by the patient **or an observer**. Diagnosis should be confirmed by a health professional with expertise in epilepsy, using available medical history, seizure description, and neurological examination. If available, EEG records and other diagnostic tools should also be used, but lack of these instruments should not preclude the diagnosis of epilepsy [16]". As stated by the commission, the clinical signs of epileptic seizures represent the most important criteria for establishing a diagnosis of epilepsy. Not only in veterinary medicine do we deal with the problem that we are dependent on an observer (the pet owner) when identifying signs of seizure activity. A substantial number of human patients as well are not able to recall what happened during a seizure.

Classification based upon seizure phenomenology does more than just serve the purpose of standardizing terminology and thereby making the comparability of data and collaborative research possible. Classifying clinical signs also ensures that many important diagnostic and prognostic clues otherwise lost, will be identified.

Since antiquity, the attempt to classify symptoms has been intended to identify a specific disease, or syndrome. The first known mention of epilepsy is at about 500 - 700 B.C. Stone tablets found in Babylon contain detailed observations of epileptic seizure types, provoking factors and postictal symptoms [49].

Veterinary epilepsy nomenclature has borrowed extensively from its human counterpart, but unfortunately has not actually agreed to standardize terminology. As a consequence, the literature on this subject is often confusing with regard to definitions and interpretations. Classification of epilepsy and epileptic seizures in humans has been established by The Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) [50,51]. The classification is based upon localisation of the seizure focus, the degree of alteration of consciousness, and possible abnormalities recorded in the EEG. Classification of epileptic seizures in dogs, based upon the guidelines of the ILAE, with an emphasis on seizure phenomenology, has been advocated by Schwartz-Porsche and by Berendt and Gram and Licht and co-workers [20,29,165].

## Classification of Epilepsy

The classification of epilepsy is based upon the underlying etiology. Classification of the epilepsies deals with three categories, *idiopathic epilepsy*, *symptomatic epilepsy* and *cryptogenic epilepsy*.

The term *idiopathic epilepsy* refers to epilepsy of unknown cause (there is no structural cerebral pathology), with a possible familial predisposition. Idiopathic epilepsy is encountered predominantly as primary generalized seizures. However, idiopathic (benign) partial epilepsies of childhood (epilepsy with partial seizures, absence of clinical or neuroimaging evidence of brain damage, characteristic interictal EEG focal sharp waves with variable location, a possible family history of idiopathic epilepsy, onset of seizures between 18 months and 13 years and spontaneous remission of epilepsy during childhood or adolescence) are well described in children and account for about 10 - 15% of epilepsy cases in this age group [52]. Among those is rolandic epilepsy (centrotemporal or midtemporal sharp waves) and epilepsy with frontal or occipital EEG changes [51,52]. Recently, a number of new idiopathic partial epilepsy syndromes with simple inheritance have been described in humans (e.g., familial partial (temporal lobe) epilepsy) [53]. Familial frontal lobe idiopathic epilepsy has been described in the Shetland Sheepdog [15]. In these dogs, the course of the disease was not benign. A substantial number of cases progressed to status epilepticus. Animals suffering from idiopathic epilepsy will interictally appear normal clinically and neurologically.

*Symptomatic epilepsy* is defined as epilepsy caused by a known/identified disorder of the CNS (focal structural cerebral pathology is disclosed) and presenting as partial seizures with or without secondary generalization. Neuropathology causing symptomatic epilepsy can be gross lesions resulting from congenital or active CNS disease, e.g., congenital malformations, storage disease, inflammatory/infectious disease, space occupying lesions, scar tissue and hemorrhage or minor pathologies such as hippocampal sclerosis, and microstructural changes of the cortex cerebri e.g., cortical neuronal loss and focal

neuronal migration disorders [54-62,175-179]. Cerebral neuronal migration disorders e.g., heterotopias or dysplasias (the majority giving rise to no other neurological signs than seizures) have been shown to represent the underlying etiology of a substantial number of partial epilepsies in humans [63-67]. Heterotopic cell clusters have also been shown to appear in the epileptic dog [68]. Degenerative lesions of the CNS e.g., hippocampus, the piriform lobe, motor cortex, frontal cortex and cingulate cortex and cerebellum have been described, post-mortem, in cats and dogs with epilepsy [15,69-71]. Reversible magnetic resonance imaging (MRI) lesions of the temporal lobe have been demonstrated in humans and in dogs following seizures [72].

The term *Cryptogenic epilepsy* (i.e., of hidden origin) is used as a designation for epilepsy with a suspected symptomatic cause which, however, remains obscure. As in symptomatic epilepsy, cryptogenic epilepsy is characterized by partial seizures. Animals suffering from symptomatic or cryptogenic epilepsy may or may not exhibit focal abnormalities interictally.

In the veterinary literature it is common to refer to epilepsy as "idiopathic epilepsy". According to the suggested classification, the term idiopathic should be reserved for those cases of epilepsy, predominantly presenting with primary generalized seizures, and in which a symptomatic origin is neither detected nor suspected [166].

### Classification of Epileptic Seizures

The clinical manifestation of an epileptic seizure reflects the field of activity in the brain areas generating the seizure and the amount and distribution of abnormal electrical activity. Epileptic seizures can be expressed as motor signs, sensory sensations, psychic experiences or autonomic disturbances [50]. Consciousness may be unimpaired, impaired or totally lost. More than one dysfunction may be present and often the clinical signs will progress within the single seizure.

The distinguishing characteristic of epilepsy is a consistent seizure phenomenology reflecting abnormal function of the entire brain or of specific (focal) cerebral areas involved in the epileptic activity. Thus the major characteristic of epilepsy is a phenomenology that occurs repeatedly in an identical manner, every time the individual animal experiences a seizure.

Epileptic seizures are divided into two main categories: Primary *generalized seizures* and *partial seizures*. *Partial seizures* are subdivided into *simple* and *complex partial seizures*. Partial seizures can spread to become *partial seizures with secondary generalization*. Regardless of the kind of seizures the animal experiences, the ictal event is brief (few seconds to few minutes). Interactions between thalamic nuclei and the neocortex working through thalamocortical and corticothalamic projections are involved in the generation of primary and secondary generalized seizures.

Primary Generalized Seizures - Primary generalized seizures are those in which the first clinical changes indicate initial involvement of both cerebral hemispheres (Fig. 1). This is reflected in the ictal EEG by a sudden and simultaneous loss of the normal electroencephalographic background activity in both hemispheres, being replaced by epileptiform discharges, representing hypersynchronous neuronal activity. There is a sudden loss of consciousness combined with a sudden onset of convulsions, without any premonitory symptoms. In the ILAE classification, primary generalized seizures are subdivided into convulsive and non-convulsive seizures and include clonic, tonic, tonic-clonic convulsions, myoclonic and atonic seizures and, in humans, absences expressed solely as repeated episodes of a few seconds' duration with impaired consciousness [50]. Absences have not been documented in dogs or cats.



Figure 1. The abnormal impulses originate from centrencephalon and the cerebral cortex. From: Gram L and Dam M. Tæt på epilepsi. Munksgaard, København, 1993. Illustrator: Lotte Clewin (with permission). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

In the past, convulsions and absences have been referred to as "grand mal" and "petit mal" respectively. This terminology is no longer used in human epileptology and should not be used in veterinary medicine, since it is non-informative.

### Partial Seizures

*Partial seizures* originate from groups of neurons localized in a specific area of the cerebral cortex (the epileptic focus) and the clinical signs reflect the functions of the area involved (Fig. 2). EEG changes indicate initial activation of neuronal networks of the area in question.



Figure 2. The abnormal impulses originate from a specific area of the cerebral cortex and do not spread. From: Gram L and Dam M. *Tæt på epilepsi*. Munksgaard, København, 1993. Illustrator: Lotte Clevin (with permission). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Simple and Complex Partial Seizures - In humans partial seizures are classified as simple if consciousness is unimpaired, and complex if consciousness is impaired. Consciousness refers to "the degree of awareness and/or responsiveness of the patient to externally applied stimuli. Responsiveness refers to the ability of the patient to carry out simple commands or willed movement and awareness refers to the patient's contact with events during the period in question and its' recall" [50].

The term aura should be used as the synonym for a simple partial seizure. In humans, by tradition, the term aura has been used to denote the symptomatology of the simple partial seizure acting as a signal/warning sign of a forthcoming seizure development into either a complex partial seizure or into secondary generalization (convulsions). In the past, signs described as aura have, in a substantial number of cases of epilepsy described in the veterinary literature, not been recognized as a part of the ictus (namely the partial onset in a partial seizure with secondary generalization), or as the ictus itself (as in partial seizures alone), but have been believed to represent a preictal event. As a consequence, these epileptic seizures have erroneously been classified as primary generalized seizures (the type of seizures predominantly characterizing idiopathic epilepsy).

In animals, signs of confusion or difficulties in recognizing the owner may be interpreted as signs of impaired consciousness. Recognizing diminished consciousness, in dogs and cats, however, can be difficult, and the patients cannot report what they are actually experiencing during a seizure. Whether it is possible from the clinical signs alone (as described by the owner and/or documented by video) - without EEG registration - to discriminate between simple and complex partial seizures in animals, is debatable.

In older terminology, complex partial seizures have been referred to as limbic seizures, psychomotor seizures and temporal lobe seizures.

Partial Seizures with Secondary Generalization - Partial seizures with secondary generalization appear to be the seizure type most commonly observed in dogs [9,23,25,28,29,165]. This is also true in the population of human adults suffering from epilepsy [73].

Secondary generalization of a partial seizure occurs when the seizure activity does not remain focal, but projects rapidly to subcortical structures (mainly thalamic nuclei) to involve other areas of the brain or the entire brain (Fig. 3).



Figure 3. Partial seizure with secondary generalization. From: Gram L and Dam M. *Tæt på epilepsi*. Munksgaard, København, 1993. Illustrator: Lotte Clevin (with permission). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

In partial seizures with secondary generalization, the clinical signs are initially characterized by the function of the anatomical site of the seizure focus, rapidly (within seconds to minutes) followed by loss of consciousness and convulsions as seizure activity spreads from the focus to involve the entire brain. In many patients, the onset of the partial seizure is very subtle and is followed by rapid secondary generalization, which can make it difficult to detect the partial onset. Therefore pet owners may not report the signs of a partial seizure onset unless questioned specifically about events preceding convulsions. Partial seizures with secondarily generalised tonic-clonic seizures with the animal retaining consciousness may occur in a very limited number of individuals. This has been described in humans [74].

*Clinical Signs in Partial Seizures* - The partial seizure itself may appear as motor signs, autonomic signs or paroxysms of behavioral signs (involving the limbic system). Localized motor activity e.g., tonic seizures of one leg or facial twitching and autonomic signs such as pupil dilatation, salivation or vomiting are fairly easy to recognize in dogs and cats whereas abnormal behavior as a sign of epilepsy represent a diagnostic (and differential diagnostic) challenge [75]. In humans, symptoms originating from the somatosensory or special sensory cortex may present, for example, as "pins and needles" sensations, numbness or visual, auditory or olfactory hallucinations/sensations (e.g., flashing light, crude auditory sensations and unpleasant odors). Psychic symptoms (most commonly occurring with impairment of consciousness: complex partial

seizures) may present as e.g., structured hallucinations, depression or rage. The most common symptoms are intense fear or terror, which may lead to running away [76]. Even though we can only hypothesize that a distortion of perception appears in animals, it seems reasonable to believe that it may be such events that give rise to the signs reported as aura, complex partial seizures, psychomotor seizures, temporal lobe seizures or even preictal phase [13,23,29,77-81]. Paroxysms of behavioral signs associated with epilepsy are frequently interpreted as anxiety or fear. The fact that these signs, in the majority of cases, are followed by convulsions is strong evidence that they represent partial seizure activity followed by secondary generalization. They should therefore **not** be regarded as preictal events.

A variety of signs of partial seizures have been reported in humans and in dogs [9,29,76,79-85].

*Prodromes* - A prodrome is a long-term indication of a forthcoming seizure. Prodromes are long-lasting (hours or days) changes of disposition in humans in the form of anxiety, irritability, withdrawal and other emotional aberrations. In dogs, the most common prodromal signs described are restlessness [29]. Owners of such dogs recognize that a seizure is about to occur within hours or days. In canine patients, up to 11% have been reported to suffer from prodromes lasting from 30 minutes to 24 hours [29]. The nature and origin of prodromes are very poorly understood.

The clinical signs of aura (the partial seizure onset of a partial seizure with secondary generalization) in animals should not be confused with the signs of prodromes, since prodromes by definition are long-lasting (hours to days) events, whereas the time frame in which the aura acts consists of a few seconds to a few minutes. When asking pet owners about prodromal signs, one should very carefully explain to the owner that the signs in question are long-lasting as opposed to signs of partial seizures (which may be followed into immediately by convulsions (secondary generalization)).

Prodromes are considered preictal events, not related to abnormal electrical activity in the EEG. It may be, however, that prodromes actually represent prolonged auras (aura continua) or non-convulsive (partial) status epilepticus. In recent years it has been possible to document EEG related ictal partial seizure activity in a number of patients experiencing prodromes (Alving J. Personal communication. Chief Neurologist, Dianalund Epilepsy Hospital, Denmark, 2002.) EEG evidence of non-convulsive status has also been documented in dogs [14].

*Postictal Signs* - The epileptic seizure may or may not be followed by a period of abnormal behavior caused by cerebral exhaustion. During this period, the post ictal phase, the animal may appear bewildered, disturbed, ataxic, tired, hungry/thirsty, blind or aggressive. The postictal phase may last from seconds to hours or even days. One should be aware that in many cases the pet owner does not distinguish ictal signs from postictal signs. As a consequence he/she may report that seizures last for a longer period of time than the few minutes' duration of the average epileptic seizure.

*Classification of Epilepsy - Future Perspectives* - In recent years a revision of the ILAE classification system from 1981 and 1989 has been discussed [50,51]. A semiological seizure classification based exclusively on ictal semiology, either as reported by the patient, by an observer or as analyzed directly by video monitoring has been proposed [86,87]. In this classification system, EEG or other test results do not influence the classification. A new ILAE classification will include more criteria for classification than descriptive terminology for ictal phenomena, e.g., classification of seizures based upon known or presumed pathophysiological and anatomic substrates [88].

It is of great interest for veterinary neurology to follow the development of a revised human epilepsy classification closely. This data can be of value for future endeavors to expand the classification of canine and feline epilepsy.

## **Diagnostic Evaluation**

*Differential Diagnosis* - The diagnoses of epilepsy in canines and felines are essentially clinical, based upon the owners' observations of seizure activity and seizure phenomenology, video documentation of seizures and diagnostic work-up aimed at distinguishing epileptic seizures from non-epileptic episodes mimicking epilepsy [13,20,23,29,89-92,165].

One should be aware that when pet owners use terms such as epilepsy, seizures, fits, attacks or convulsions they may indicate various clinical phenomena not at all associated with these terms. It is therefore crucial to investigate closely what kind of event the pet owner actually has witnessed.

The primary question, when presented with a canine or feline patient experiencing episodes leading to a suspicion of epilepsy, is whether these are of epileptic nature or not. Many systemic disorders of organic, metabolic, endocrine, toxic or behavioural origin can appear clinically as imitators of epilepsy. However, these diseases will normally be detected provided a thorough diagnostic work-up is done.

Special interest should be given to a number of paroxysmal disorders, which may easily be confused with epilepsy. Among those, narcolepsy, cataplexy and syncope may represent a diagnostic problem as they involve signs that are very common in epilepsy.

Narcolepsy is characterized by disturbance of consciousness accompanied by sudden falling (atonia). The duration of sleep is usually short (a few minutes to 20 minutes). Cataplexy is a short, sudden reduction or loss of muscle tone. Signs may vary

from weakness or head drop to sudden fall to the ground. Attacks last from seconds to a few minutes. Consciousness is fully retained during the episodes. Syncope is an episodic interruption of consciousness due to a diminished blood flow to the brain (the animal "faints"). The causes of syncope may vary greatly, but the clinical signs are rather uniform. The temporary complete arrest of cerebral perfusion causes the animal to collapse and pupils to dilate, followed by convulsive movements. Most commonly, these movements differ from tonic-clonic convulsions by only taking the form of tonic extension of the trunk, clenching of the jaw, or mild clonic jerks of the limbs or trunk and twitching of the face.

Among the most common are vasovagal syncopes (provoked by conditions which favour peripheral vasodilatation such as excitement, fear or pain), cardiac syncopes (often caused by a sudden reduction in cardiac output due to dysrhythmia) and tussive syncopes (caused by respiratory conditions e.g., laryngitis or chronic bronchitis, where an increase in intrathoracic pressure interferes with the venous return to the heart).

Diagnostic Work-up - When working with suspected epilepsy patients, the initial clinical work-up should, as a minimum, include a detailed description of the events witnessed by the pet owner, a full physical and neurological examination, hematology and serum biochemistry, urine analysis and survey radiographs of the thorax and the abdomen (to exclude primary neoplasms with the potential to metastasize to the brain). In some cases the diagnosis of epilepsy can be excluded based upon the history or the laboratory test results alone. If no extra cranial causes can be identified, the diagnosis of epilepsy is highly possible.

The next question to ask is what kind of seizures the patient does experience (classification). This is best investigated by analysing seizure episodes and seizure phenomenology. A standardized questionnaire should be used when collecting and recording detailed information on the events reported by the pet owner [75]. The questionnaire should be given orally. The patient history should focus on the previous medical history, including clues of a possible birth trauma and information regarding earlier occurrence of head trauma or febrile disorders affecting the brain. The history should also include age at first seizure, seizure frequency, and a detailed description of seizure development and seizure phenomenology. Since veterinarians are dependent on second hand information, it is crucial to secure an accurate and detailed report from the owner. The subjective nature of the owner's interpretation is minimized by the use of a standardized questionnaire focussing on ictal events. The questionnaire ensures that details that might otherwise be missed are recorded and help to distinguish ictal from postictal events. If the episodes witnessed by the pet owner include convulsions, in the majority of cases the owner will naturally focus on this very dramatic event. However, if questioned thoroughly regarding circumstances preceding convulsions, the owner may describe signs identifying the seizure as partial with secondary generalization.

Since veterinarians rarely have the opportunity to observe seizures in the canine and feline epilepsy patient, home video or video recording during hospitalisation, represent an excellent supplement to the descriptions of seizures given by the owners. "EEG records and other diagnostic tools should also be used, if available, but lack of these instruments should not preclude the diagnosis of epilepsy. EEG contributes, but does not always confirm a diagnosis of epilepsy: An abnormal EEG must not be considered as a requisite for inclusion since it could be normal (or indicate non-specific abnormalities) in epileptic subjects" [16]. The source of the EEG is electrical potentials generated by cortical neurons. If EEG registration takes place sufficiently close to the populations of abnormal firing neurons, they will produce characteristic pathological changes in the EEG. The disadvantage of surface EEG registration is that only activity from surface areas that are anatomically accessible are recorded. Therefore, an abnormal electroencephalogram can support the diagnosis of epilepsy whereas a normal electroencephalogram does not exclude this diagnosis. EEG is helpful in discriminating between partial and generalized epileptic discharges. Also the EEG may identify a suspected seizure focus [8,10,14,15,180]. Intracranial EEG (electrodes implanted on the dura mater) has proved effective in detecting the epileptic focus in a Shetland Sheepdog [167].

To answer the question of the possible cause of seizures, the following diagnostic methods can be chosen with the specific aim of uncovering seizure etiology: CNS pathology pointing towards a diagnosis of symptomatic/cryptogenic epilepsy may be disclosed by neurological deficits detected at the neurological examination. When dealing with partial seizures (with or without secondary generalization) one should always consider the possibility of identifying cerebral pathology. In the diagnostic work-up of human epilepsy patients, prolonged video-EEG studies and imaging of the brain (CT/MRI) have become a routine investigation in patients with clinical evidence of a partial seizure onset (suspected symptomatic/cryptogenic epilepsy). Computed tomography (CT) and magnetic resonance imaging (MRI) has proven very helpful in the diagnostic management of epilepsy in animals [58,59,72,168]. Cerebrospinal fluid examination should be examined in cases pointing to an active cerebral disorder since CNS pathology may be reflected in the cerebrospinal fluid [57,168].

### **Diagnostic Work-up in Patients Suspected of Epilepsy - Protocol**

- Detailed history (including previous medical history)
- Detailed description of events experienced (questionnaire) + home video
- Clinical examination
  - Assess cardiovascular function (if abnormal findings order EKG and ultrasound)
  - Assess respiratory system (if abnormal findings order endoscopy)
- Hematology and serum biochemistry
- Urine analysis
- Survey radiographs of thorax and abdomen
- Neurological examination
  - If neurological signs localized to the brain: CSF, brain scan
- EEG

### **Disorders causing signs commonly confused with epilepsy**

- Cardiovascular disorders (including syncope)
- Respiratory disorders (laryngeal/tracheal/bronchial dysfunction), including syncope
- Narcolepsy
- Cataplexy
- Anemia
- Organic disease (e.g., hepatic/renal dysfunction)
- Hyperthyroidism (cat)
- Hypoglycemia (e.g., insulinoma)
- Electrolyte unbalances
- Neuromuscular disease (e.g., myasthenia gravis)
- Intoxication
- Abnormal behavior

### **Signs of Prodromes**

Any warnings of forthcoming seizures i.e., long-lasting changes (30 minutes - several days) in behaviour before seizures emerge

### **Ictal events (short <2 - 3 minutes episodes)**

Duration of signs

### **Signs of Primary Generalized Seizures**

Does the animal experience convulsions

Is consciousness lost from the onset of the seizure

Are convulsions present from the onset of seizure

Are convulsions tonic, clonic or initially tonic followed by a clonic phase

Does the animal experience atonic episodes

### **Signs of Partial Seizures**

Episodic localised motor signs

Paroxysms of behavioural signs: Short (<2 - 3 minutes) stereotyped episodes of change in the dogs behaviour e.g., restlessness, anxiety, attention seeking, hyperactivity, "hallucinations" such as catching or watching imaginary objects, unprovoked aggression, signs of fear, manic behaviour, abnormal vocalising.

Episodic autonomic signs e.g., salivation, vomiting, pupillary dilatation

## **Partial Seizures with or without Secondary Generalization**

If any signs of partial seizure activity - do these signs occur isolated or are they followed by convulsions

Duration of signs

## **Postictal Signs**

Duration of the postictal phase

Description of behaviour during the postictal phase (does the dog appear e.g., disoriented, "blind", hyperactive, exhausted or aggressive)

## **Long-term Therapy of Epilepsy**

General Therapeutic Considerations - The overall consideration is if or when to start therapy in patients with epilepsy. It is commonly stated that early treatment of epileptic seizures significantly increases the success rate with respect to seizure control - an assumption "borrowed" from human medicine. In humans, this assumption has now been contradicted by the results of large population-based cohort surveys, showing that long term outcome is not influenced negatively by the number of seizures experienced prior to institution of treatment [93,94].

The decision of when to start antiepileptic treatment depends on a wide range of factors. Patients that are especially at risk of developing new seizures, e.g., patients with status epilepticus as the first indication of epilepsy or animals with symptomatic epilepsy caused by active CNS disease, should be treated early. In animals experiencing cluster seizures and prolonged seizures, early treatment is also recommendable due to the increased risk of neuronal damage. The pet owners' attitude toward treatment and the question of owner compliance must be taken into consideration. Some owners will tolerate a limited number of seizures a year, while others will accept nothing less than seizure freedom. Some owners may find it hard to accept that epilepsy treatment involves long-term, maybe life-long, treatment and as a consequence may even consider euthanasia as an alternative to treatment. Finally, when antiepileptic treatment is first instituted, the disadvantages of the potential adverse effects of the antiepileptic drug(s) must be counterbalanced against the goal of obtaining seizure freedom.

Antiepileptic Drugs - Ideally, the antiepileptic drug for long-term treatment has a long elimination half-life (needs only dosing once or twice a day), is well tolerated, possesses no adverse effects and is inexpensive. To date, no anticonvulsants have proven to fulfill all these criteria.

Several attempts have been made to apply the broad variety of human antiepileptic drugs in animals. In people, the new anticonvulsants licensed for use as monotherapy or polytherapy are generally well tolerated [95]. It is therefore tempting to assume that they would be effective in canines and felines also. These drugs include carbamazepine, oxcarbazepine, valproic acid, gabapentin, feldbamate, vigabatrin and nimodipine among others. Their pharmacokinetic properties particularly the elimination half-life, toxicity, adverse effects, and to some extent the cost of a potential treatment [96-103] make them generally not applicable in animals. This section shall therefore address only phenobarbital, potassium bromide, primidone, phenytoin and benzodiazepines.

Phenobarbital - Although an "old" drug in veterinary medicine, phenobarbital still holds the position as a first drug of choice. This is a safe anticonvulsant with a high efficacy and a long elimination half-life (dogs: 42 - 89 hours, Beagle 32 +/- 4.6 hours. Cats: 34 - 43 hours), that is generally well tolerated by dogs and cats [104-107].

Several antiepileptic drugs, including barbiturates and benzodiazepines, enhance GABA action at its primary site, the GABA-benzodiazepine chloride-channel complex [108]. Phenobarbital thereby inhibits spreading of seizure activity and elevates seizure threshold.

Phenobarbital is lipid soluble, easily absorbed (maximal plasma concentrations are reached 4 - 8 hours after oral administration) and crosses biological membranes readily. Pharmacokinetic studies have found a bioavailability of 86 - 96% [105]. Protein binding is about 45% [109]. Phenobarbital is for the most part metabolized in the liver. Approximately one third is excreted unchanged renally [96]. The drug possesses strong liver enzyme inducing properties. Elevated liver enzymes, due to enzyme induction, are therefore to be expected [110]. In phenobarbital-treated patients the only reliable measurement of hepatic status is a liver function test (bile acids monitored fasting and postprandial).

Adverse effects include sedation, ataxia, polyphagia, polydipsia, incontinence and hyperactivity. Most animals will develop tolerance to the medication causing the unwanted side effects to disappear within the first weeks of treatment. Hyperactivity is mostly associated with low serum phenobarbital values and can in many cases be eliminated by increasing the drug dosage. The recommended oral dosage of phenobarbital in dogs and cats is 3 - 5 mg/kg/day (one daily dosage or divided and administered twice a day). The ability to metabolize phenobarbital varies greatly between individuals, and the given drug dosage shall, therefore, never be taken as an expression of the effectiveness of the drug [111]. Instead, serum concentration of phenobarbital must be measured, and the drug dosage must be adjusted according to the actual amount of drug in the serum and clinical observations of seizure frequency. Because of the long half-life, it takes about two weeks for steady state to occur

(the time when phenobarbital can first be monitored). Timing of blood collection is not important. It has been shown that there is no therapeutically relevant change in serum phenobarbital concentrations throughout a daily dosing interval [112]. The therapeutic serum concentration (the level within which the drug is expected to be therapeutically active and where toxicity should not be expected) is 15 - 45 µg/ml/65 - 150 µmol/l [113]. Confusingly enough, patients might be seizure free despite serum values ranging beneath the lower therapeutic serum concentration. In this case, the dosage of phenobarbital should only be adjusted if seizure freedom is lost. The serum phenobarbital concentration should always be measured if seizures reoccur (in patients that have achieved seizure freedom), if a known constant (low) seizure frequency suddenly begins to increase and whenever drug dosages are changed. If using polytherapy with phenobarbital and potassium bromide, the phenobarbital dosage can in some cases successfully be decreased when potassium bromide has reached steady state.

Bromide (potassium bromide/sodium bromide) - Bromide, the first human anticonvulsant (introduced around 1850), was reintroduced for the treatment of refractory epilepsy in children in the nineteen-eighties, and has been used as an add-on drug in refractory canine epilepsy for the last two decades [114]. Most data on bromide in veterinary medicine has been on potassium bromide. The only indication for using sodium bromide is in patients with compromised renal function or adrenal insufficiency. About 25% of phenobarbital resistant canine epilepsy patients become seizure free on polytherapy with phenobarbital and bromide [115,116]. Bromide can also be used as a first drug of choice, e.g., in patients with hepatic dysfunction. There is only limited knowledge (data) of bromide (and its potential adverse effects) in cats. It is therefore recommended that this drug, until further data on cats are available, be used only in the treatment of canine epilepsy [169]. The anticonvulsant action of bromide is not really known. The drug is believed to act through hyperpolarization of postsynaptic membranes [117]. Bromide salts (potassium bromide/sodium bromide) are rapidly absorbed after oral administration. They are unbound to plasma proteins and can therefore diffuse freely across membranes. Bromide has a very long elimination half-life (about 28 days). Steady state will therefore occur about four months after therapy has been instituted. Excretion occurs through the kidneys and is dependent on concomitant chloride intake. Attention should therefore be given to the dietary influence of the excretion of bromides. A high dietary chloride content shortens the elimination half-life causing decreased therapeutic serum bromide concentrations and thereby loss of therapeutic efficacy [118]. The recommended oral dosage for bromide is 20 - 40 (60) mg/kg /day (one daily dosage). The therapeutic range of bromide in dogs is 100 - 200 mg/dl when potassium bromide is used as an add-on drug and 250 - 300 mg/dl when used as monotherapy [102]. Mild adverse effects are similar to the ones described for phenobarbital. Signs of bromide toxicosis include ataxia, depression, stupor, anisocoria, muscle pain, dermatological signs such as rash and nodular pustular skin lesions, and gastrointestinal signs such as anorexia, vomiting and constipation [119,120].

Primidone - Primidone is oxidized to phenylethylmalonic acid (PEMA) and phenobarbital. More than 85% of the anticonvulsant effect can be attributed to phenobarbital [104]. The drug is well tolerated by both dogs and cats [121]. Hepatotoxicity has occurred in dogs after long-term treatment with primidone [122,123]. Primidone is also a more expensive drug than phenobarbital. Phenobarbital should therefore be preferred to primidone.

Phenytoin (diphenylhydantoin) - Phenytoin is a potent and effective anticonvulsant. Due to its pharmacokinetics, however, this drug is not a useful drug in dogs and cats [124]. In dogs, the lack of efficacy arises mainly from problems to maintain effective plasma concentrations despite of multiple daily dosing [96]. A slow release formula may solve this problem in the future. It is important to know that in cats the drug is eliminated very slowly. As a result, there is an increased risk of accumulation of the drug to toxic levels even at low dosages [125]. Phenytoin may be used for status epilepticus in dogs (2.0 - 5.0 mg/kg given as a slow IV injection).

Benzodiazepines - Benzodiazepines, although excellent anticonvulsants, has no use in long-term treatment of canine epilepsy, due to a short elimination half-life and a rapid (5 - 7 days) development of tolerance to their anticonvulsant effect. In the past, diazepam has been used as a first drug of choice in cats. Severe hepatotoxicity has, however, been associated with this drug in cats, thereby making long-term treatment with diazepam controversial in this species [126]. Thus the primary indication for benzodiazepines is in the management of acute epileptic seizures and status epilepticus. Benzodiazepines are further discussed in the section on Status Epilepticus.

In conclusion, when taking the pros and the cons of the above drugs into consideration, we are mainly left with only two drugs for long-term treatment of dogs, namely phenobarbital and bromide and one for cats, namely phenobarbital.



Complications Associated with Long-term Phenobarbital (primidone) and Potassium Bromide Treatment - Both phenobarbital and primidone can cause hepatotoxicity [113,122,123]. Chronic phenobarbital therapy has the potential to influence thyroxine and thyroid-stimulating hormone. Phenobarbital has been shown to decrease the concentration of T4 without causing clinical signs of hypothyroidism - TSH tests responses were normal [127,128]. Other studies have shown decreased T4 values and increased TSH values without clinical evidence of hypothyroidism associated with phenobarbital therapy [110,129]. Potassium bromide does not seem to influence thyroid function [170]. In the study of Gieger and co-workers serum ALP, ALT, cholesterol, serum albumin and GGT were also monitored. No changes were found for serum albumin and GGT whereas ALP, ALT and cholesterol values were significantly increased. Chauvet and co-workers [130] found that ALP and ALT values increased whereas serum albumin and cholesterol decreased over time [130]. In another study of effects of phenobarbital on serum biochemical tests in dogs it was concluded that phenobarbital causes variable increases in ALP, while bilirubin, cholesterol, albumin and TP concentrations remained normal [131]. A rise in liver enzymes associated with phenobarbital administration has also been demonstrated by other authors [181]. Hojo and co-workers report that long term treatment with phenobarbital significantly induced hepatic CYPs and plasma AGP (hepatic cytochrome P450 and alpha 1-acid glucoprotein) in dogs [171].

Neutropenia and thrombocytopenia can occur with phenobarbital and primidone treatment. A drug-induced agranulocytosis of an immunologic origin (as suggested in humans) may be the underlying cause of the damage to the hematopoiesis, but the precise mechanism is not known [132].

An increased risk for epilepsy patients of developing fatal acute pancreatitis has been shown in a case control study of 70 dogs [133]. The risk of developing pancreatitis is higher in dogs receiving polytherapy with phenobarbital and potassium bromide than in dogs receiving phenobarbital as monotherapy [134]. Superficial necrolytic dermatitis has been reported in dogs receiving long-term phenobarbital administration [182].

Therapeutic Failure - Therapeutic failure may occur because therapy is initially not successful; therapy is successful initially but then becomes less effective or ineffective; or because therapy is only partly successful (seizure frequency and/or seizure severity is reduced but seizure freedom is not achieved).

Common reasons for therapeutic failure

- Dealing with a potentially "difficult" patient (cluster seizures, prolonged seizures).  
Incorrect diagnosis (it is not epilepsy)
- Incorrect choice of antiepileptic drug
- Incorrect dosage of the antiepileptic drug
- Failure to monitor drug levels
- Owner non-compliance
- Presence of epilepsy plus newly developed systemic disease (liver/kidney)
- Patient has gained weight (drug dosage needs to be adjusted)
- The animal has developed a tolerance to the drug (phenobarbital/benzodiazepines)
- Monotherapy is insufficient

Withdrawal of Antiepileptic Drugs - Withdrawing antiepileptic drugs may be considered, if an animal has been seizure free for more than one year.

In humans, epilepsy in remission due to treatment (drug induced remission) is defined as "a prevalent case of epilepsy with no seizures for  $\geq 5$  years and receiving antiepileptic drugs at the time of ascertainment" [16]. Withdrawal of antiepileptic drugs may be considered in human adults who have been seizure free with medication for 5 years. Due to the shorter lifetime of dogs and cats, a time frame of one year of seizure freedom seems reasonable [25]. When considering withdrawal of anticonvulsant medication one must gradually decrease the drug dosage over a longer period of time. A period of 6 - 12 months has been recommended [20].

Before making this choice the potential risk for seizure reoccurrence should be balanced against the advantage of decreasing the risk of the long-term adverse effects that may be experienced with antiepileptic drugs.

Instructions to the Owners - Dogs with epilepsy are very time consuming patients due to the need for close patient monitoring. When dealing with medical treatment of epilepsy it is critical that the owner is instructed very carefully. Patients should be reevaluated yearly and more frequently (+ additional telephone contact 2 - 3 times a year) if seizure frequency increases, if seizure freedom is lost, if signs of systemic disease appear or whenever the owner needs advice.

The owner should be instructed to keep a seizure diary (seizure calendar) to bring along to re-examinations as this insures that important information regarding seizure frequency is not lost. The veterinarian should remember to record dates for prescriptions of drugs and to record the amounts of medicine prescribed.

It is crucial to give the owner a realistic idea of what to expect in terms of side effects and therapeutic success. The owner may thus respond more positively to the question of a possible lifelong antiepileptic treatment and to the fact that seizure freedom in a percentage of cases cannot be achieved. Important information to be given to the owner is that the initial period of treatment can be difficult, with respect to side effects; NEVER to withdraw drugs or change drug dosages without consulting the veterinarian (since this entails a substantial risk of seizure reoccurrence and possible status epilepticus); to always contact the veterinarian in case of unexpected side effects, and always to bring the animal to the veterinarian if signs of status epilepticus occur.

### **Non-medical Treatment for Epilepsy**

Epilepsy Surgery - In humans, surgical management of intractable partial epilepsies has become an efficacious and safe alternative in patients with partial onset seizures (medical therapy resistant or experiencing intolerable side effects). This procedure, however, requires that the epileptic focus be identified - using intracranial EEG, MRI and SPECT scan among others. There are only a few papers on surgical treatment for seizures (not including surgical management of space occupying lesions) in canine epilepsy [135,136]. Computed tomography- guided stereotactic procedures have been used for brain biopsy in dogs. Perhaps similar procedures might be applicable in animals with an identifiable epileptic focus in the future [137].

Vagal Nerve Stimulation - Animal and human studies have shown that vagal nerve stimulation in some cases can prevent or reduce seizures [138,139]. This non-pharmacological treatment may be considered for treatment of medically intractable partial seizures in humans. The exact mechanism of action of vagal nerve stimulation remains unknown. The vagal effects on the EEG, are probably mediated by the NTS (nucleus of the solitary tract) parabrachial-thalamic pathway [140]. Vagal nerve stimulation by digital ocular compression has been investigated as a treatment modality for aborting epileptic seizures in a study of seven dogs. The results of this study suggest that vagal nerve stimulation may be beneficial in some canine epilepsy patients [141]. This has been supported by the results of a study by Munana and co-workers [172].

Ketogenic Diet - The ketogenic diet (a high fat, moderate protein, low carbohydrate diet), utilized as an alternative treatment in some children epilepsies, has been proposed as a therapeutic alternative in the management of canine epilepsy. The anticonvulsant effect is exercised through inducing ketosis and acidosis - similar to what is observed in starvation. In a study of Puchowicz and co-workers the level of ketosis achieved in dogs given the ketogenic diet was lower than the level measured in children whose seizures were controlled by the ketogenic diet [142].

### **Status Epilepticus (SE)**

Status Epilepticus (SE) is a life threatening condition that requires immediate treatment. Small animals with convulsive SE are frequently admitted to the emergency clinic and this condition is one of the most dramatic acute disorders encountered in small animals [143,144]. Signs of CNS damage after SE can persist for weeks, months or be permanent.

In 1993, SE was defined by the Epilepsy Foundation of America's Working Group on Status Epilepticus as "more than 30 minutes of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between seizures" [145]. A revised operational definition defines convulsive SE as "generalized convulsive status in adults and older children (>5 years old) refers to  $\geq 5$  min of continuous seizures or two or more discrete seizures between which there is incomplete recovery of consciousness [146]. To apply this definition of SE seems more practical, given that the "normal" tonic-clonic seizure terminates within 5 minutes. The effects of long-lasting seizure activity such as neuronal injury and the risk of dying from the complications of SE may be prevented by early treatment [147-149].

Clusters of seizures (serial seizures), in which there are two or more seizures within a period of minutes to many hours (and where the patient regains consciousness between seizures), should not be confused with status epilepticus. On the other hand clusters of seizures may still represent a potential emergency situation. In cases of continuous serial seizures the patient should therefore be treated as an SE patient.

Classification of SE - Status Epilepticus (SE) can be classified as non-convulsive SE (partial status: limited to partial seizure activity) and convulsive SE.

Non-convulsive SE (simple or complex partial SE) will only be touched on briefly here. This form of SE is scarcely documented in animals as it requires acute EEG monitoring and/or clinical recognition of impaired consciousness. Partial SE has been documented to occur in dogs [14,143].

In cases where partial seizure signs continue or where signs interpreted as postictal are intensive and long-lasting (days), one should consider the possibility that the animal may be in a partial SE.

### Convulsive Status Epilepticus -

*Why Does Convulsive SE Happen?* Animals presenting in SE can be divided into two groups: Patients with known epilepsy and patients for whom SE is the first epileptic event.

In animals presenting with SE as the first epileptic event, SE is often precipitated by cerebral trauma, an intracranial space occupying process, inflammatory CNS disease, intoxication, or acute metabolic disturbance. In animals with an established diagnosis of epilepsy, SE can occur at any time due to the disease itself, but provoking factors such as non-compliance, change in drug regimen, drug toxicity, infections (fever), organ dysfunction, hepatic enzyme induction and weight gain, among others, should also be taken into consideration.

In 58% of human SE patients, SE represents the first indication of epilepsy. Patients at high risk include individuals suffering from symptomatic epilepsy (focal cerebral pathology/partial seizures with or without secondary generalization), intractable epilepsy and frontal lobe epilepsy [150]. This has been shown to be true for the canine also [173]. Prevalence for SE or cluster seizures as a percentage of total hospital admissions of dogs over a period of five years has been reported to be 0.44% [143].

The Pathophysiology of Convulsive SE - The pathophysiology of convulsive SE is closely associated with the duration of the prolonged seizure activity [151,152]. A distinction of SE into early SE (the first 30 minutes) and late SE can be made, based upon the severity of the physiologic and neurophysiologic changes increasing the more prolonged the status becomes [147-149,151,153].

In early SE, the compensatory phase (0 - 30 minutes), the brain manages to compensate for the increased metabolic demand for oxygen and glucose by increasing blood flow greatly. Cardiac output, cardiac rate and blood pressure rise and an increase in circulating catecholamines occurs, resulting in a hypersympathetic autonomic reaction causing hyperpyrexia, bronchial secretion, salivation and vomiting. Additionally, excessive muscle activity contributes to the dramatic rise in temperature often associated with SE [147]. Lactic acidosis from excess anaerobic metabolism develops from the onset of status, due to increased neuronal and muscular activity, accelerated glycolysis, tissue hypoxia, respiratory depression and catecholamine release. Other metabolic disturbances are hypoglycemia, hypo and hyperkalemia and hyponatremia.

During the decompensatory phase (after 30 - 60 minutes of continuous seizure activity) the system fails to meet the continuous high metabolic demand of the epileptic brain. When cerebral autoregulation breaks down, cerebral blood flow becomes dependent on systemic blood pressure, resulting in hypotension, decreased cerebral blood flow, decreased metabolism and thus ischemia and neuronal death.

During the decompensatory phase, systemic and cerebral hypoxia, pulmonary hypertension and edema and cardiac arrhythmia are likely to develop. Cardiac arrhythmias in SE are a result of direct seizure-associated autonomic activation, catecholamine release, hypoglycemia, acidosis and electrolyte disturbances. In late SE, the cumulative hypoxic damage will affect most organ systems with an increasing danger of multiorgan failure. The increase in intracranial pressure will eventually lead to cerebral edema.

Management of Convulsive SE - Animals with SE are high-risk patients! Treating them as intensive care patients and following a standardized protocol therefore greatly increases their survivability. Overall, the importance of having a protocol cannot be stressed enough. One may prefer one anticonvulsant to another, e.g., different benzodiazepines, but what is most important is that the veterinarian is familiar with the drug, that the drug is available in the clinic, and that the complications of SE are addressed.

The patient should, first of all, be stabilized. The airway should be secured, oxygen supplied and an intravenous line (large vein - large catheter) should be established. Anticonvulsants should be administered early (within 5 minutes) and aggressively (blood for monitoring serum levels of phenobarbital should be drawn before administering drugs). Monitor clinical and neurological status, blood pressure, ECG, temperature, blood gasses, pH, blood hematology and biochemistry. Treat complications. Decrease temperature in cases with hyperthermia. In animals with hypoglycemia, glucose should be administered intravenously. The lactic acidosis will reverse with effective control of respiration and motor seizure activity (only on rare occasions is treatment with bicarbonate necessary).

As soon as the patient is stabilized the etiology of the status should be established and investigated, since acute CNS disease calls for therapy aimed at the primary lesion. History should, at a minimum, include information regarding any signs of disease prior to status, previous medical problems, and drugs or toxin exposure.

Anticonvulsive Drugs in SE - The ideal antiepileptic drug in status epilepticus is available for intravenous administration, fast working (highly lipid soluble - fast penetration to the CNS), does not possess sedative side effects, does not interfere with cardiovascular or respiratory functioning and can be used for long-term treatment. Unfortunately such a drug does not exist. Benzodiazepines are the drugs that come closest to the properties mentioned above. Diazepam, clonazepam or lorazepam are the initial drugs of choice due to their rapid onset of action and their effectiveness. Diazepam is metabolized in the liver to

desmethyl diazepam, temazepam and oxacepam. All metabolites are pharmacologically active. Diazepam is highly lipid soluble, and highly protein-bound (94 - 96%). The elimination half-life is about 2 - 4 hours in the dog and 15 - 20 hours in the cat. [154,155], Diazepam penetrates to the CNS faster than lorazepam (within 1 minute after IV injection) due to the higher lipid solubility. The disadvantage of diazepam is that due to this property, the concentration (and effectiveness) of diazepam also decreases more rapidly. Lorazepam is actively retained in the brain and has a longer duration of protection. The unwanted side effects of both drugs are sedation and respiratory depression. Lorazepam produces prolonged period of sedation as compared to diazepam. There is only limited experience with lorazepam [156]. Diazepam can be administered IV, intranasally or rectally [28, 158]. Diazepam is administered as a bolus IV (0.5 - 1 mg/kg) or rectal (1 - 2 mg/kg) and can be repeated once after 5 - 10 minutes.

Continuous benzodiazepine administration in prolonged SE should be avoided. Due to the prolonged seizure activity itself influencing cerebral mechanisms, functional changes occur in GABA-A receptors causing a diminished response of diazepam during prolonged SE [159]. Additionally the risk of side effects increases dramatically with continuous administration due to distribution/redistribution of the drug to/from the lipid compartment. The initial treatment with benzodiazepines should therefore, be followed by a fixed dose of phenobarbital (IV bolus 5 - 10 mg/kg) to secure a long-lasting neuronal protection. Phenobarbital is a very effective anticonvulsant. The disadvantage of the drug is that it penetrates slowly to the CNS (15 - 20 minutes after IV injection). It is therefore not recommendable as a first drug of choice in SE. Phenobarbital naïve patients can be started on a loading dose: Total mg IV = (kg body weight) x (0.8 L/kg) x 20 (this would equal 16 mg/kg) given gradually. The initial treatment with phenobarbital is followed by phenobarbital infusion (constant rate of 2 - 6 mg/dog/hour). Chronic treatment with phenobarbital has shown to reduce the effect of diazepam, presumably due to an increased hepatic clearance [160].

Barbiturates possess the same side effects as benzodiazepines. Adding barbiturates to the above, therefore, increases the risk of serious side effects such as cardiac and respiratory depression.

In cases of refractory SE, the animal must be anesthetized with pentobarbital (barbiturate induced coma). Propofol may also be used to induce anesthesia in refractory SE. Propofol, however, has proven to possess both convulsant and anticonvulsant qualities [161,162].

Steroid therapy is recommended if brain edema is suspected, dexamethasone 0.25 mg/kg (can be repeated 1 - 3 times a day for up to 3 days). In cases of infectious CNS disease the treatment with steroids must be based on an individual assessment of the pros and cons. Once the animal has been seizure-free for 8 - 12 hours, emergency antiepileptic drug treatment can be weaned off slowly.

Therapeutic Failure in SE - In cases of therapeutic failure, the clinical, paraclinical and medical parameters should be reassessed. Common errors leading to therapeutic failure are: The dosage of antiepileptic drugs is not sufficient, continuous injections with diazepam in late SE, failure to identify the underlying cause or failure to identify the complications of the SE itself.

Instructions to Owners - Any successfully treated episode of SE should be followed by steps to prevent SE from happening again. When recovering from SE, continued oral treatment with antiepileptic drug(s) should always be considered (monotherapy or polytherapy in known epilepsy patients already treated with one drug). The owners of animals at risk of recurring SE can be supplied with diazepam for intranasal or rectal administration at home.

**Patients with Status Epilepticus are intensive care patients !**

Status Epilepticus - Protocol		
Time Table	Clinic	Medical Treatment
0 - 5 minutes	<ul style="list-style-type: none"> <li>History</li> <li>Clinical examination</li> <li>Neurological examination</li> <li>Observe seizure activity</li> <li>Supply oxygen</li> <li>IV-line (large catheter)</li> <li>Hematology, serum biochemistry and blood gasses</li> <li>ECG, pulsoxymetry</li> </ul> <p><b>Identify etiology</b></p>	<ul style="list-style-type: none"> <li>(Diazepam 1 mg/kg IV /rectal bolus)</li> </ul>
5 - 15 minutes	<ul style="list-style-type: none"> <li>If hypoglycemia: 50% glucose (central vein)</li> <li>May treat acidosis</li> </ul>	<ul style="list-style-type: none"> <li>Diazepam 1 mg/kg IV</li> <li>Can be repeated once after 5 min.</li> </ul>
15 - 30 minutes	<ul style="list-style-type: none"> <li>Intensive care patient monitoring</li> </ul>	<ul style="list-style-type: none"> <li>If Diazepam stops seizures: Administer phenobarbital (5 - 10 mg/kg (up to 20 mg/kg) as a bolus (100 mg/min)) - to prevent recurrence of seizures</li> <li>If seizures continue: Administer phenobarbital (5 - 10 mg/kg (up to 20 mg/kg) as a bolus (100 mg/min)) - to stop seizures</li> </ul>
30 - 60 minutes	<ul style="list-style-type: none"> <li>Continuous patient monitoring</li> <li>Intubate</li> <li>Ventilate (O<sub>2</sub>)</li> <li>Regulate blood pressure</li> <li>Observe/treat cerebral edema (methylprednisolone/mannitol)</li> <li>Continuous treatment of complications</li> </ul>	<p>If SE continues after IV phenobarbital: Induce coma with general anesthesia:</p> <ul style="list-style-type: none"> <li>Pentobarbital (2 - 8 mg/kg IV as a bolus)</li> <li>Propofol (4 mg/kg)</li> <li>Methylprednisolone (30 mg/kg/ IV as a bolus – continuous treatment with 15 mg/kg every 2. hour for 24 hours)</li> <li>Mannitol (1g/kg)</li> </ul>

Remember to always consider long-term treatment with anticonvulsive drugs

### Closing Remarks

Epilepsy is a most challenging disease with respect to diagnostic approach and therapeutic management. Most animals can live a normal life with antiepileptic drugs. It is important to always remember that, being the family of an epileptic animal will, in many cases, represent an emotional stress factor and that owner counselling - is likely to be inevitable, to prevent the owner from giving up.

## Epilepsy: Medical history and seizure symptomatology - check list [PRINT](#)

Patient ID:..... Name:.....

Breed:.....

Sex:.....

Neutralized:.....

Age:.....

Weight:.....

Epilepsy among close

relatives.....

Known birth

complications.....

Previous head

trauma.....

Previous CNS

infection.....

Age at first

seizure.....

Seizure

frequency.....

Distribution of seizures (single/clusters)

.....

Circadian distribution of seizures (during sleep, upon awakening, at day, during activity)

.....

Seizure provoking factors (e.g., stress, excitement)

.....

Seizure related to hormonal fluctuations or hormonal imbalance

.....

### Seizure development as described by the owner

.....

.....

.....

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## Paroxysmal Disorders (6-Feb-2003)

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Several disorders are characterized by episodic, paroxysmal attacks during which affected animals may be acutely and dramatically incapacitated. Animals do not lose consciousness and are clinically normal between attacks. The pathophysiology of these disorders involves (or is considered to involve) abnormal neurotransmitter function, and microscopic changes are often not observed within the central nervous system. Episodic falling and muscle cramping, sometimes termed hyperkinesia (i.e., excessive motility or muscular activity) or muscular hypertonicity, are bizarre, paroxysmal neurological disorders that have been recognized in several breeds of dogs. Other paroxysmal neurological disorders include several sleep abnormalities of which narcolepsy is the best recognized.

An outline of this chapter is as follows:

### **Hyperkinetic Disorders**

- Episodic Falling
- Scotty Cramp

### **Sleep Disorders**

- Narcolepsy
  - Cataplexy
- Miscellaneous Sleep Disorders
  - Narcoleptic Hypersomnia
  - Periodic Leg Movements During Sleep
  - Rapid Eye Movement Sleep Disorder
  - Age-related Changes in Sleep-wake Rhythm in Dogs

### **Miscellaneous Paroxysmal Disorders**

- Familial Reflex Myoclonus
- Myokymia
- Syncope

### **Episodic Falling**

Episodic falling or hypertonicity is a well-recognized paroxysmal disorder in Cavalier King Charles Spaniels in the UK [1,2], and has been seen in the United States and Australia [67]. After a variable period of exercise, affected animals develop a peculiar bounding, pelvic limb gait in which the limbs may be abducted and appear stiff. Other signs may include a bunny-hopping gait, arching of the spine, vocalization and collapse. There is no loss of consciousness. Some affected dogs assume a "deer-stalking" posture, with increasing limb stiffness, falling, and legs held in extensor rigidity [2]. Episodes appear to be triggered by stress, apprehension, and excitement. Signs are typically first observed between 3 and 7 months of age. Animals are neurologically normal between attacks, which appear to be a life-long event. Affected dogs do not respond to anticholinesterases, but slight, temporary improvement may occur following diazepam treatment. A greater clinical improvement is reported following treatment with the benzodiazepine drug clonazepam which enhances GABA neurotransmission [67,70]. In one trial, clonazepam (at 0.5 mg/kg tid) resulted in almost complete remission of signs over a 2-year period [70]. Frequency of attacks is reportedly increased in some dogs using the antiepileptic drug carbamazepine (Tegretol) [1]. Results of hematology, blood chemistries, and electrodiagnostic testing are within normal limits. There is no evidence of lactic acidosis. No light microscopic lesions are seen in the central nervous system (CNS), peripheral nervous system (PNS), or viscera. Skeletal muscle appears normal microscopically, apart from presence of small vacuoles between myofibrils in some fibres stained with toluidine blue [2]. Histochemical staining using myosin ATPase, succinic dehydrogenase, and phosphorylase is normal. Ultrastructural alterations, however, have been reported in skeletal muscle,

which include dilatation and proliferation of sarcotubular elements, mitochondrial swelling and degeneration of cristae, and tubular proliferations in the region of the triads [3]. Wright stated that she was uncertain if the morphological changes were causally related to the clinical signs [2]. The pathogenesis of this paroxysmal condition remains enigmatic, although both genetic and neuropharmacological factors may be involved. In one study, 7 of 8 dogs were males and 5 had a common male ancestor that suggested an inherited trait [2]. It has been suggested [67,70] that this disorder has some similarities to hyperexplexia (startle disease) in people, a hereditary (autosomal dominant) pathological exaggeration of the normal startle response to auditory, somesthetic or visual stimuli which sometimes results in falling [68,69].

### **Scotty Cramp**

This is an inherited paroxysmal neurological disorder with a recessive mode of transmission in Scottish Terrier dogs [4-6]. Pharmacological studies suggest that the disorder is associated with a deficiency or relative deficiency of the inhibitory neurotransmitter serotonin (5-hydroxytryptamine), although serotonin brain content appeared normal in one study of affected dogs [7,8]. Anti-serotonin agents (e.g., p-chlorophenylalanine and amphetamine) markedly increase the severity of clinical signs, the intensity of which are reduced by a variety of drugs that increase cerebral serotonin concentration including tryptophan, phentolamine, nialamide and 5-hydroxytryptophan administration [5,9]. In one case report, ingestion of an excessive quantity of methionine induced Scotty cramp-like signs in a 2 year old Scottish Terrier that had not previously been seen to exhibit signs of the condition [10]. It was suggested that the methionine may have increased levels of the bi-methylated methionine compound, S-adenosylmethionine, which in turn might have acted as a methyl donor leading to an increased rate of serotonin methylation and consequently resulting in decreased levels of active CNS serotonin. Other studies suggest that the condition results from a complex interaction between serotonin and prostaglandins within the CNS [11] since anti-prostaglandin compounds (e.g., aspirin, phenylbutazolidin, penicillin G, flumixin meglumine, and indomethacin) increase the severity of clinical signs in affected dogs.

Clinical signs may be elicited by exercise, excitement, stress, and poor health. The condition may occur in animals at any age, however, signs tend to be more prevalent in young dogs less than 6 months of age. Affected dogs appear normal when at rest or at the beginning of exercise. As the exercise continues, clinical signs are usually observed that progressively increase in severity. Initial signs may be abduction of the thoracic limbs or arching of the lumbar spine, followed by pelvic limb stiffness, occasional catapulting of the pelvic limbs into the air, falling and curling into a ball, with the tail and pelvic limbs tightly flexed against the body. Respiration may momentarily cease and facial muscles may be contracted. Animals do not lose consciousness. Signs usually remit within 10 minutes. Multiple episodes may occur over a 24 hour period. The disorder is usually non-progressive.

Although there are no structural changes observed in the CNS, PNS, or in muscle of dogs with this episodic disorder, dural adhesions, meningeal hemorrhage, and bony irregularities causing dural and cortical impressions have been noted in one study involving affected Scottish Terriers [12]. These changes were seen in 10 of 12 young dogs (6 weeks to 18 months of age) and in 5 of 8 older dogs (3 to 11 years of age), suggesting possible inherited abnormalities that potentially affect the area of the motor cortex and account for the sporadic clinical signs under circumstances (e.g., stress, excitement, etc.) that increase arterial blood volume and brain volume/intracranial pressure [12]. To the author's knowledge, this theory has not been validated by other researchers.

Diagnosis may be based on historical information revealing a family history of cramping and on the clinical signs, since all laboratory tests are within normal limits. Signs can be induced using methylsergide, a serotonin antagonist, administered orally at a dosage of 0.3 mg/kg, and the animal exercised two hours later. Treatment consists of daily oral dosing of acepromazine maleate (0.1 to 0.75 mg/kg every 12 hours), or diazepam (0.5 mg/kg every 8 hours). Vitamin E (125 IU/kg/day) may also be effective [13]. Sometimes, behavioral modification or environmental change may be sufficient to avert clinical signs [13]. Note that clinical signs in older dogs may be induced or increased by concurrent disease.

A very similar condition has been reported in 2 young Dalmatian dogs, as well as in a Cocker Spaniel and a Wirehaired Terrier [14]. Muscle cramping or spasms involving the hindquarters, usually after but sometimes during exercise, and lasting for up to 5 minutes, is often seen in Norwich Terriers [15]. Muscle cramping characterized by weakness and exercise intolerance reportedly occurs sporadically in field-trial English Springer Spaniels with hereditary phosphofructokinase deficiency (see glycogenosis type VII).

### **Narcolepsy**

Human narcolepsy is a neurological disorder associated with abnormalities of rapid eye movement sleep and of sleep-wake control [16,17]. The clinical hallmarks are excessive sleepiness and cataplexy (an abnormal manifestations of rapid eye movement sleep [18]), although sleep paralysis and hypnagogic hallucinations may occur as well [19]. Narcolepsy occurs sporadically in dogs [20-26] and rarely, in cats [20,27]. In animals, although excessive daytime sleepiness may be seen (especially in the colony-housed narcoleptic dogs [28]), cataplexy is often the dominant clinical sign, which is characterized by sudden paroxysmal attacks of flaccid paralysis (muscle atonia) with conservation of consciousness, that may last from a

few seconds to more than 20 minutes, with sudden termination of signs [22,24,25]. Respiratory and ocular muscles tend to be spared, and swallowing and cough reflexes appear to be intact during cataplectic attacks. There is no fecal or urinary incontinence, no excessive salivation and no tonic rigidity of muscle. The attacks are frequently induced by excitement, such as eating, playing, sexual activity, or presence of owner or another dog. Attacks can be reversed by an external stimulus, such as petting or calling the animal's name. The frequency of attacks may vary from one every other day, to several hundred per day. Signs generally appear in affected animals prior to 6 months of age [29], although initial attacks can occur in mature animals. Results of a recent study using narcoleptic Doberman puppies showed that cataplexy onset (mean age around 10 weeks) corresponded to the emergence of adult-like REM sleep. The cataplectic attacks were more severe in the female puppies.

The pathogenesis of this disorder remains uncertain; however, an imbalance between cholinergic (e.g., hyperactive) and catecholaminergic (e.g., hypoactive) neurotransmitter systems within the CNS appears to be involved [30-34]. One mechanism might be through reduction in rate of locus coeruleus discharge (it is hypothesized that locus coeruleus activity contributes to the maintenance of muscle tone in waking; the rate is decreased by prazosin, an alpha 1 antagonist, and physostigmine, a cholinesterase inhibitor, both of which precipitate cataplexy) [35]. Some studies show that increased dopamine transmission mediates the wake-promoting effects of amphetamine-like stimulants [36], while others demonstrate preferential involvement of adrenergic systems in the control of cataplexy [37,38]. Recent studies also point to hypocretins (orexins) as important sleep-modulating neurotransmitters [18,39,40]. The hypocretins (orexins) are two novel neuropeptides (Hcrt-1 and Hcrt-2), derived from the same precursor gene, that are synthesized by hypothalamic neurons [72-74]. In addition, autoimmunity is considered by some researchers to play a role in the development of narcolepsy [41]. In human narcolepsy, most patients have non-familial (sporadic) narcolepsy, although one predisposing genetic factor is an HLA (human leukocyte antigen) gene of low penetrance [42]. Narcolepsy has been reported in many canine breeds including Doberman Pinscher, Miniature Poodle, Labrador Retriever, Dachshund, St. Bernard, Beagle, Afghan, Airedale, Welsh Corgi, Irish Setter, Malamute, Springer Spaniel, Standard Poodle, Wire-Haired Griffon, Australian Shepherd mix, Chihuahua-Terrier mix, Giant Schnauzer, and Rottweiler. Molecular studies have shown a degree of genetic heterogeneity in canine narcoleptics [43]. Autosomal recessive mutations have been reported in Doberman Pinschers and Labrador Retrievers involving a *canarc-1* gene with full penetrance [19], tightly linked with a marker homologous to the human micro-switch immunoglobulin gene (but not linked with the dog leukocyte antigen complex) [44], and a hypocretin (orexin) receptor 2 gene (*Hcrtr2*) [18,39] (the *canarc-1* mutation is a deletion of the hypocretin receptor 2 gene, although the mutation in these breeds is in a different region of the same gene). A milder mutation has also been identified in familial narcolepsy in Dachshunds [43]. No mutations in the *Hcrtr* gene were found in other, unrelated narcoleptic dogs [43]. Hypocretin mutations have been documented in human narcoleptics along with massive loss of hypocretin neurons and increase in glial fibrillary acidic protein in the hypothalamus [40,45,46]. Narcolepsy is also believed to be hereditary in Poodles [29].

There have been only a few recent reports of brain changes in canine narcoleptic patients. In a histochemical study using the amino-cupric silver stain on brain sections from canine narcoleptics, increased axonal degeneration was observed in the forebrain, including amygdala, basal forebrain (including the nucleus of the diagonal band, substantia innominata, and preoptic region), entopeduncular nucleus, and medial septal region [47]. Reactive neuronal changes were found in the ventral amygdala. Axonal degeneration was maximal at 2 - 4 months of age, while the number of reactive cells was highest at 1 month of age. These degenerative changes occurred before or at the time of onset of clinical signs. In another study, increased numbers of cholinergic neurons, identified by NADPH-diaphorase histochemistry, were found in the brains of narcoleptic dogs [48]. Microscopic brain lesions have occasionally been reported in cases of spontaneous narcolepsy in dogs. In light of the recent research on hypocretin neuropeptides and their effects on hypothalamic neurons, it is of interest that cataplectic-like attacks were observed in a 10 month old female Wirehaired Pointing Griffon with a hamartoma of the hypothalamus [49]. A coincidental relationship was considered in a 10 month old Argentine Dogo with narcolepsy and diffuse encephalitis in the forebrain and marked necrotic lesions in the ventral pontine area attributable to canine distemper encephalitis [50]. In a Giant Schnauzer with narcolepsy, malformation of the aqueduct of Sylvius and atrophy of the periventricular tissue in the midbrain were found at necropsy, but again, the authors were uncertain if these lesions were causally related to the narcolepsy [26]. Cataplectic episodes were also reported in a 12 week old Cairn Terrier puppy with multisystemic chromatolytic neuronal degeneration involving many nuclei in the brainstem, as well as in spinal cord, cerebellar nuclei, and sensory ganglia [51] (see Multisystem Neuronal Abiotrophy in Cairn Terriers).

Diagnosis is typically based on clinical signs. Attacks can be induced in most affected animals by exercise or eating. Signs can be alleviated for up to 45 minutes using an intravenous imipramine challenge test, at a dose of 0.5 mg/kg. Atropine sulfate (0.1 mg/kg, IV) is also reported to be a useful diagnostic test, providing immediate, temporary remission of signs for up to 3 hours [24]. The most common electrophysiological finding associated with narcolepsy/cataplexy in dogs is the rapid eye movement (REM) onset sleep and the shortened sleep cycle. During cataplectic attacks, there may be simultaneous

occurrence of REM sleep-like phasic events such as rapid eye movements, muscular twitching, variable vocalization, facial grimacing and chewing movements.

Prognosis is guarded. The disease is not in itself life-threatening and it may not get significantly worse with time. In humans, typical treatment for narcolepsy-cataplexy includes amphetamine-like stimulants for sleepiness and antidepressant therapy (e.g., non-sedating tricyclic antidepressants and serotonin/norepinephrine-reuptake inhibitors) for abnormal REM sleep (i.e., cataplexy, sleep paralysis, and hypnagogic hallucinations) [17,52]. For long-term treatment, animals may respond very favorably to tricyclic antidepressants, such as imipramine hydrochloride. Recommended dosage ranges from 0.5 to 1.5 mg/kg, PO tid or bid. Side effects of this drug in dogs include nervousness and sleepiness, which appear to be dose related. Methylphenidate hydrochloride (Ritalin), at 0.25 mg/kg, PO sid or bid, may also be effective. In a cataplectic Longhaired Dachshund (in which neither imipramine or methylphenidate were ineffective), treatment with dexamphetamine sulfate, at a total oral daily dosage of 5 mg, resulted in complete remission of clinical signs; however, treatment was stopped because of unacceptable behavioral side-effects (excessive sniffing of the ground, climbing into inaccessible places, hyperactivity, and refusal to eat) [25]. Although some dogs with severe signs early in life can show considerable amelioration of signs as adults, most dogs require lifetime treatment. In people, prolonged remissions are followed eventually by recurrence if drug treatment is stopped.

Several experimental drugs have been tested in colony narcoleptic dogs. These include CG-3703, a potent thyrotropin releasing hormone (TRH) analog, at 16 to 28 mg/kg PO, which significantly reduced cataplexy and daytime sleep, without changes in general behavior, heart rate, blood pressure, rectal temperature, blood chemistry or thyroid function [53]. In additional studies, systemically administered hypocretin-1 (*Hcr1-I*) had a dramatic effect on canine narcoleptics (increased activity level, longer waking periods, a decrease in REM sleep without change in nonREM sleep, reduced sleep fragmentation and a dose-dependent reduction in cataplexy were noted) [54]. In other canine studies, both acute and chronic oral administration of sulpiride (300 mg/dog, 600 mg/dog), a dopamine D2/D3 receptor antagonist, also significantly reduced cataplexy without noticeable side effects [55].

### **Miscellaneous Sleep-related Disorders**

Narcoleptic Hypersomnia - This condition, characterized by inappropriate and excessive daytime sleepiness, lethargy, and difficulty in arousing from sleep, was observed in a 6 month old Labrador Retriever dog [56]. Rapid eye movement and paddling within a few minutes of sleep onset were occasionally observed. Physical and neurological examinations, blood (including arterial blood gas) and urine analysis, and EKG were normal. Food-elicited cataplexy testing was negative. Electroencephalography revealed excessive slow wave (6 - 10 Hz, 20 - 45  $\mu$ v) activity. The dog was successfully treated using the tricyclic antidepressant protriptyline (Vivactil), at 10 mg PO per day. Continued treatment was necessary.

Periodic Leg Movements During Sleep - Results of a recent study indicated that narcoleptic dogs exhibited jerky, unilateral or bilateral slow leg movements during sleep characterized by repetitive dorsiflexions of the ankle, lasting 0.5 - 1.5 s, and occurring at regular intervals of 3 - 20 s [57]. These movements were considered to be similar to an idiopathic sleep disorder in humans, termed periodic leg movements during sleep (PLMS). Pharmacological studies suggested that altered dopaminergic regulation in canine narcolepsy may play a critical role in both cataplexy and PLMS. Presumably, the above-mentioned treatment aimed at controlling cataplexy should also control PLMS in narcoleptic dogs.

Rapid Eye Movement Sleep Disorder - Another, sporadic sleep disorder has been reported in a 15 month old cat in which violent seizure-like movements (pelvic limb movements sufficiently vigorous to propel the cat from a couch to the floor) occurred only during REM sleep (demonstrated by simultaneous electroencephalographic and electromyographic recordings) [58]. The episodes were not responsive to phenobarbital and a cause was not determined. The cat was easily aroused from these paroxysmal episodes and appeared immediately alert and without evidence of confusion. The cat, which was otherwise healthy, continued to have normal motor behavior during wakefulness and the abnormal sleep activity for 2.5 years after first presentation.

Age-related Changes in Sleep-wake Rhythm in Dogs - Results of recent studies indicate abnormalities in wakefulness (fragmentation of wakefulness in the daytime and a sleep disruption in the night), slow wave sleep (increased during daytime), and paradoxical sleep (reduced) in older dogs [75]. These changes may be associated with altered autonomic balance in the aged dogs.

### **Miscellaneous Paroxysmal Disorders**

Familial Reflex Myoclonus - This disorder has been reported in Labrador Retrievers puppies [59,60]. The pathogenesis is unknown. Clinical signs develop in puppies at about 3 weeks of age and are characterized by paroxysmal muscle spasms and progressive muscle stiffness to the point where affected animals are unable to walk or rise without assistance. Animals



lay in lateral recumbency and develop generalized extensor rigidity and opisthotonus in response to handling, voluntary activity and auditory stimuli. During severe episodes, respiratory distress and apnea can be observed, along with facial and masticatory muscle contracture and arching of the spine associated with paraspinal contractions. The extensor rigidity mimics generalized strychnine poisoning. Animals tend to relax in a quiet environment (in fact, at rest, affected animals appear normal). There is no evidence of muscle pain or percussion dimpling. Neurological deficits are not detected. Electromyographic recordings after various stimuli are characterized by intermittent bursts of giant polyphasic action potentials (0.5 - 15 mV). There are no myotonic discharges and motor nerve conduction velocities are normal. Results of urinalysis, hematology, blood chemistries, and muscle and nerve biopsies are within normal limits. No lesions are seen in the brain or spinal cord. Prognosis is guarded to poor. Therapeutic trials with diazepam (at 0.5 to 2.0 mg/kg PO, tid) alone or with phenobarbital (at 2.2 to 5.0 mg/kg PO bid) provides partial relief from the tonic spasms, although episodes can still be induced. Intravenous pentobarbital abolishes all signs of rigidity. The disorder may be genetic since in one study, the grandsire of the affected litter had sired 2 previous litters containing similarly affected pups. In the two reports to date, affected to normal puppy ratios have been 2:5 and 3:5 [59,60]. A defect in glycine, the major inhibitory neurotransmitter in the spinal cord, or altered genetic regulation of the spinal cord glycine receptor, has been suggested as the basis for this disorder [60].

**Myokymia** - A novel disorder clinically characterized by intermittent, rhythmic, vermicular movement of muscle groups in all four limbs leading to collapse into lateral recumbency (but without loss of consciousness) has been reported in a Yorkshire Terrier [76]. Signs began around 11 months of age. No neurological abnormalities were detected. Hematology and blood chemistries were normal apart from a mild increase in serum creatine phosphokinase levels. No lesions were seen in a muscle biopsy. Dramatic improvement in signs occurred with procainamide therapy (62.5 mg PO, tid). Signs returned on cessation of therapy.

Dramatic, paroxysmal attacks may be seen in animals with seizures (see epilepsy) and syncope. Seizures are the clinical manifestation of functional disturbances of the brain caused by hyperexcitable cortical neurons and animals may or may not lose consciousness [61]. **Syncope** refers to rapid loss of consciousness and postural tone caused by reduced cerebral blood flow [62]. It is most commonly associated with cardiovascular problems (e.g., dysrhythmias) but also may be related to autonomic perturbations, such as vasovagal syncope and carotid sinus sensitivity [63,64,77]. Defecation syncope and pulmonary thromboembolism has been reported in a cat [78]. Primary neurological disorders are extremely unlikely to cause syncope [62]. Painful, episodic muscle cramps affecting thoracic and pelvic limbs have been reported in two standard Poodles diagnosed with hypoadrenocorticism (the dogs were being treated with fludrocortisone acetate and prednisone) [71]. Neurological examination was normal between episodes. Serum biochemical abnormalities included hyperalbuminemia, azotemia, hyponatremia, hypochloremia, and hyperkalemia. Changing treatment to desoxycorticosterone pivalate resolved the electrolyte abnormalities and the episodes of muscle cramping in both dogs. Episodic weakness, collapse, and paralysis may occur with hyperkalemic myopathy. Episodic weakness, exercise intolerance, and acute onset of a stiff-stilted gait may be seen in animals with hypokalemic myopathy. Paroxysmal general body tremor and collapse into sternal recumbency associated with exercise or excitement has been reported in a young Great Dane with central core myopathy. Note that some forms of hyperkinesia [65] and episodic states, such as tail chasing [66], represent behavioral disorders. Hyperkinesia also occurs often in cats with hyperthyroidism. Periodic infarctions as a result of intravascular lymphomas may result in episodic neurological signs in dogs (see Infarction). Intermittent forelimb lameness has been reported in dogs with hypothyroidism (see Hypothyroid Neuropathy).

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## Electrodiagnostic Evaluation (24-Feb-2003)

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Electrodiagnostic procedures have contributed to the certainty of diagnosis of a variety of neurological and neuromuscular diseases in animals. Widespread use of electrodiagnosis is limited by equipment costs and training of personnel. However, many of these procedures are used routinely in case work-ups in veterinary colleges or specialty practices. The purpose of this chapter is to present a brief review of the basic electrophysiology and methodology for a wide range of electrodiagnostic techniques. Examples of normal and abnormal recordings are presented, but the reader is referred to the literature for more specific information [1-22] or detailed descriptions of electrodiagnostic findings in specific neurological diseases. In addition, the American Association of Electrodiagnostic Medicine ([www.aaem.net](http://www.aaem.net)) provides instructional materials and courses on electromyography at both basic and advanced levels.

### **Physiological Basis for Electrodiagnostic Studies**

#### **Resting Membrane Potentials**

The phospholipid-containing membranes of muscle and nerve cells separate intracellular and extracellular fluids that differ in composition. Membranes also separate charged molecules such that the voltage measured in the interior of the cell is negative 70 to 90 mV relative to the exterior. Because this electrical gradient has the potential to do work, it is called a *resting membrane potential* (RMP). Some active membrane transport systems called pumps co-transport ions in opposite directions

at different rates, for example, the sodium pump which transports sodium and potassium. Because this transport contributes to the RMP, these pumps are called *electrogenic*. The RMP in a single cell can be measured with microelectrodes but not with electrodes on the surface of the body. Many of the procedures in clinical electrophysiology need to be non-invasive. Consequently, far field potentials are recorded with surface or needle electrodes which are distant from the actual electrical generators.

### Action Potentials

When sufficiently intense stimuli are applied to excitable cells, either nerve or muscle, the membrane potential reverses (depolarization) and then spontaneously recovers (repolarization). These changes are brought about by the influx of sodium (depolarization) followed by the efflux of potassium (repolarization). Ion fluxes are initiated by alterations in membrane permeabilities associated with changes in specific ion channels located within the membrane. The tendency for sodium and potassium to travel down their electrochemical gradients through open channels is the basis for the *action potential* that is propagated along the axolemma (by continuous or saltatory conduction) or along the sarcolemma.

Action Potentials in Single Cells - An understanding of the initiation and propagation of an action potential in a single excitable cell is basic to many of the procedures in clinical electrodiagnostics. The action potential must be recreated at synapses, the junctions between neurons or between neurons and muscle cells. Action potentials are characterized by features such as amplitude, duration, and conduction velocity. The amplitude of an action potential from a single cell is measured in microvolts, and may be missed altogether if the recording electrode is not close to the active cell and/or the gain of the amplifier is too low. Therefore, most clinical electrodiagnostic procedures are based on recording transmembrane changes in large numbers of cells.

Compound Action Potentials - When excitable cells are simultaneously active, a *compound action potential* may be recorded. The amplitude of a compound potential is dependent on the number of participating cells and their respective amplitudes. The duration of the compound potential is a reflection of *synchrony*. Similar cells that discharge simultaneously will produce a brief duration whereas a long duration will be caused by dissimilar cells discharging synchronously or similar cells discharging asynchronously. In electrodiagnostic recordings, the terms *potential* or *response* may be used to refer to a recording of a single action potential, a compound action potential, or a combination of action potentials and postsynaptic potentials.

### Postsynaptic Potentials

The usual means of communication between excitable cells is the synapse. A synapse between a neuron and a skeletal muscle cell is called the *myoneural* or *neuromuscular junction*. In response to neurotransmitters, postjunctional membranes in neurons may produce *excitatory postsynaptic potentials* (EPSP) or *inhibitory postsynaptic potentials* (IPSP). Postjunctional excitation in a skeletal muscle, in response to the release of acetylcholine by the motor axon terminal, is referred to as an *end-plate potential* (EPP). The EPP is a local, non-propagated potential. Postsynaptic potentials are also a source for bioelectric activity that can be recorded with surface or needle electrodes.

### Technical Aspects of Recording Electrical Activity

#### Differential Amplifier: Digital and Analog

Because bioelectrical signals are so small, some form of amplification is required. Amplification of biological signals is commonly achieved with a *differential amplifier*. This type of amplifier has two inputs; the magnitude of the output represents the difference between the inputs. For many electrodiagnostic procedures, the inputs are provided by an active electrode and a reference electrode. The active electrode is placed near the activity to be recorded and the reference is placed in a distant inactive area. Because the differential amplifier attenuates activity that is common to both inputs, it helps to eliminate unwanted background electrical activity or "*noise*" which is a source of artifact.

Bioelectric events are usually recorded in one of two forms, *analog* or *digital*. The output of an amplifier may be routed to a pen-writing recorder or oscilloscope; the display is an analog of the original physiological activity. Such a device presents the activity continuously in time. Discrete and discontinuous sampling of events at a predetermined rate is the first step toward recording information in digital form. One important advantage of the digital form is that high speed mathematical operations can be performed on the data during or after the recording. Digitally recorded potentials can be stored on computer and reconstructed later.

The frequency range over which an amplifier can amplify biopotentials without distortion is called its *frequency response*. High and low frequency filters allow the frequency response to be adjusted for optimal recording of the response. These filters attenuate unwanted noise with frequencies below and above the low and high frequency settings. For each type of electrodiagnostic procedure, the appropriate filter settings should be utilized consistently. Improper settings can alter the amplitude, shape and/or latency of responses. Differences in these settings among laboratories make comparisons of results more difficult.

### **Volume Conduction and Electrode Types**

Many of the bioelectric events described in this chapter are recorded at a distance (far-field) from the *generators* of the actual activity. The generator is the source of the current, and the surrounding tissue and fluids are the volume through which it is conducted. Selection of the proper electrode is critical to successfully recording any bioelectric event. Surface electrodes can be difficult to apply to the skin of animals, although adhesive electrodes, metal disc electrodes and alligator clips have been used. Needle electrodes are commonly used. Needle electrodes can be placed subcutaneously or can be inserted deeper into muscle or placed near nerves. *Monopolar* electrodes are referenced to a second electrode at another site. With *concentric* electrodes, the active electrode is embedded in the core of the needle and insulated from the shaft which serves as the reference. *Bipolar* electrodes have both the active and reference electrode embedded within the core of the needle. Other specialized types of electrodes include contact lens electrodes for electroretinography.

The interface between the recording electrode and the tissue creates resistance to electrical current. Because of the types of circuits involved in electrodiagnostic recording systems, this type of resistance is more properly termed *impedance*. The impedance of the electrode-skin interface should be kept as low as possible and should be evenly matched between recording and reference electrodes in order to avoid *impedance mismatch*. This precaution, together with a high input impedance of the recorder, provide for the reliable recording of biopotentials.

### **Volitional, Spontaneous and Evoked Activity**

Electrical activity recorded from excitable tissue can be *voluntary*, *spontaneous* or *evoked*. Voluntary activity occurs when an animal consciously performs some activity, such as moving a limb. Spontaneous activity can be recorded without voluntary participation or the use of an external stimulus, for example, electroencephalograms. Evoked responses (or "evoked potentials") represent the electrical response to an external stimulus, typically delivered at a specific intensity and rate (frequency). With such exceptions as testing of olfactory, visual, and auditory systems, most evoked responses are elicited by short pulses of electric current.

### **Triggered and Non-triggered Signals**

For evoked potentials, amplifiers are *triggered* by the stimulus to begin recording for a preset period of time, termed the *analysis time*. In some protocols, a delay circuit is used to begin the recording at a fixed time after stimulus application. The time that the amplifier records activity is sometimes referred to as the *window*. A recording of spontaneous activity usually requires a wider recording window.

### **Signal Averaging**

Many evoked responses are extremely small, with a poor signal-to-noise ratio. *Signal averaging* is a widely used technique to enhance the biopotential and reduce noise. If multiple responses are electronically averaged, the amplitude of the evoked response is increased in direct proportion to the number of samples. The background noise, which is random, is decreased by the square root of the number of responses. The number of repetitions that need to be averaged is determined by factors such as the response amplitude and the amount of noise. Although a set number of repetitions may be used in a protocol, it is up to the examiner to determine when an optimal response has been recorded. Higher numbers of repetitions do not equate with higher quality of recording. In some instances, the use of large numbers of repetitions can diminish the quality of the recording.

### **Calibration**

The biopotentials discussed in this chapter are primarily rapidly occurring, low amplitude signals. Because many are far-field recordings, they are much smaller than the potentials recorded directly from single cells with microelectrodes. Most electrodiagnostic equipment is designed to record potentials in the millivolt (mV) and microvolt ( $\mu$ V) range. Time calibrations are usually in milliseconds. Most equipment provides on-screen cursors and computer programs that enable accurate measurements.

### **Audio Monitoring**

For needle electromyographic (EMG) examinations, audio monitoring of signals is utilized. Biopotentials are taken from the system amplifier and fed to an audio amplifier and a speaker. Some specific EMG potentials, such as fibrillation potentials, have distinctive sounds by which they can be identified.

### **Electrical Activity in Muscle**

#### **Voluntary Activity in Muscle**

Motor Unit Potentials - Electromyography (EMG) is the study of electrical activity in nerve and muscle. The basic functional

unit of normal skeletal muscle is the *motor unit*, which consists of a ventral horn cell (also termed a *lower motor neuron*, LMN) and the muscle cells (myofibers) which are innervated by its motor axon. When a LMN is activated, an action potential is propagated along its axon (motor nerve fiber), chemically recreated at end-plates, and then propagated along muscle cell membranes prior to muscle contraction. The composite electrical activity in muscle cell membranes in a motor unit is called a *motor unit potential* (MUP). Typical MUPs recorded from a dog with a monopolar electrode are shown in (Fig. 1). The size of a single MUP depends upon the type and size of the motor unit and the proximity of the unit to the recording electrode.

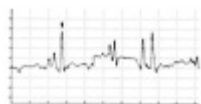


Figure 1. Motor unit potentials (MUPs) recorded from the triceps brachii muscle of a dog during voluntary contraction. Arrow identifies one of several MUPs. Horizontal division = 1.2 msec; vertical division = 0.5 mV. (Included with permission from: M. H. Sims. In: *Electrodiagnostic evaluation*. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994; 349-368.). - To

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Electromyograms are often recorded in anesthetized or tranquilized animals to eliminate unwanted volitional activity and movement artifacts. Stoic animals and debilitated animals often will tolerate needle EMG examination provided the examiner is patient and handles the animal carefully. Volitional movement may be induced by reflexes or weight shifting. In some neurogenic diseases, MUPs can have an increase in duration and amplitude due to increased innervation ratios caused by collateral sprouting and reinnervation. These unusually large MUPs are referred to as *giant motor unit potentials*. The clinical interpretation of alterations in the duration, amplitude and shape of MUPs is part of the training for personnel who perform EMG. Recently, EMG has been incorporated into the technique for the administration of botulinum toxin (Botox). In these cases, EMG is used to pinpoint the site of botulinum toxin injection at the end plate region within the muscle [23].

Interference Patterns - Normal volitional muscle contraction is brought about by the activation of large numbers of motor units. *Recruitment* is the process of adding motor units to ones that are already active in order to increase the force of contraction. The pattern of muscle contraction during normal physiologic activity is called an *interference pattern* because the individual MUPs "interfere" with each other in a recording (Fig. 2).

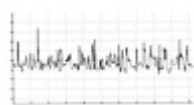


Figure 2. Partial interference pattern in a cat semitendinosus muscle as a result of volitional flexion of the stifle joint. horizontal division = 1.2 msec; vertical division = 0.5 mV. (Included with permission from: M. H. Sims. In: *Electrodiagnostic evaluation*. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994; 349-368.). - To view this image in full size go to the IVIS website at

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Depending upon the intensity of muscle contraction, the interference pattern may be *complete* or *incomplete*. The interference pattern can be recorded from specific muscles with intramuscular monopolar needle electrodes or fine wire electrodes. Both types of electrodes are insulated except for the tip of the needle or wire. The characteristics of the interference pattern can aid the clinician in determining whether the disorder is myopathic or neuropathic. For instance, in peripheral neuropathies, the interference pattern tends to be reduced.

### Spontaneous Activity in Muscle

Spontaneous activity in muscle, when it occurs, may be initiated in the LMN, the nerve root, the peripheral axon, the end-plate, or the muscle membrane itself. If skeletal muscle is not volitionally or reflexively activated, it is electrically quiescent. Most spontaneous activity is indicative of neuromuscular abnormalities.

Miniature End-Plate Potentials - Each skeletal muscle cell is innervated by a single branch of the LMN axon at a synapse referred to as the *end-plate*. In the absence of LMN activation, spontaneous activity in muscle is only recorded at locations within muscle where there is a high concentration of end-plates. These electrical discharges may be recorded by needle electrodes as *end-plate noise* which consists of large numbers of *miniature end-plate potentials* (MEPP). The electromyographer should be careful to distinguish between normal end-plate noise and fibrillation potentials.

Insertion Potentials - Other than end-plate noise, normal muscle membranes are electrically silent if there is no LMN activity. However, when a needle electrode is inserted into or moved in a normal healthy muscle, it is accompanied by electrical activity called *insertion potentials*. Insertion potentials are caused by the mechanical stimulation of muscle fibers and usually cease when needle movement ceases. As described below, insertion potentials may be prolonged in neuropathic or myopathic disorders and mixed with other abnormal potentials such as positive sharp waves and fibrillation potentials. Insertion potentials may be reduced in severely atrophied muscle or muscle with fibrosis.

Fasciculation Potentials - *Fasciculation* is the spontaneous twitch that occurs when motor units or parts of neighboring motor units discharge. Electrically, fasciculations have durations, amplitudes and other characteristics similar to MUPs.



Fasciculations are likely caused by ephaptically activated muscle fibers ("cross-talk") as a result of discharge in pacemaker fibers in either nerve or muscle. Fasciculations can sometimes be observed through the skin. Fasciculation can be seen in a variety of diseases affecting nerve and muscle, and infrequently in degenerative diseases affecting the spinal cord gray matter.

Fibrillation Potentials - *Fibrillation potentials* (FP) are spontaneous bi- or triphasic potentials that occur in neurogenic and myopathic disorders (Fig. 3). Fibrillation potentials represent the discharge of single muscle fibers. The sound of these potentials from a loudspeaker has been likened to "eggs frying" or "rain on a tin roof".

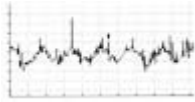


Figure 3. Fibrillation potentials occurring spontaneously in the triceps muscle of a dog as a result of nerve fiber loss in the radial nerve. Arrow indicates one of several fibrillation potentials. Horizontal division = 10 msec; vertical division = 97.7  $\mu$ V. (Included with permission from: M. H. Sims. In: Electrodiagnostic evaluation. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St

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This potential is a consistent electrical hallmark of partially or completely denervated muscle. The amplitude of fibrillation potentials ranges from 50 - 350  $\mu$ V with durations of 1 - 2 msec. In cases of nerve damage, FPs do not occur immediately after denervation. Instead, FPs appear in the denervated muscle after a latent period that is proportional to the length of remaining axons distal to the site of a nerve lesion. Their onset may be preceded by periods of increased insertional activity. Once these potentials appear in denervated muscle, their rate of occurrence increases over a period of several weeks, and they persist until muscle is reinnervated or until no viable muscle fibers remain. Fibrillation potentials are also seen in myopathic disorders such as muscular dystrophies, polymyositis, and dermatomyositis. Their origin is related to oscillating membrane changes or irregular prepotentials caused by membrane instability. In neuropathies characterized by demyelination rather than axonal degeneration (Wallerian degeneration), FPs tend to be absent.

Positive Sharp Waves - *Positive sharp waves* (PSWs) are characterized by an initial positive phase followed by a more gradual negative-going phase (Fig. 4). Although these potentials make a lower pitched sound than fibrillation potentials and usually have a lower discharge rate, they are currently considered to represent a type of fibrillation potential.



Figure 4. Positive sharp waves (PSWs) mixed with fibrillation potentials recorded from a forearm flexor muscle in a dog. Arrow identifies one of several PSWs. Horizontal division = 10 msec; vertical division = 97.7  $\mu$ V. (Included with permission from: M. H. Sims. In: Electrodiagnostic evaluation. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994; 349-368.). - To

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Complex Repetitive Discharges - Complex repetitive discharges (formerly named *bizarre high frequency discharges* or *pseudomyotonic discharges*) consist of polyphasic potentials that discharge spontaneously at a high frequency. Within the train of discharges, each potential may have the same morphology (Fig. 5).

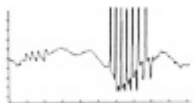


Figure 5. Complex repetitive discharges recorded in an extensor muscle of the forearm of a dog. Horizontal division = 10 msec; vertical division = 97.7  $\mu$ V. (Included with permission from: M. H. Sims. In: Electrodiagnostic evaluation. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994; 349-368.). - To view this image in full size go to the IVIS website at

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Such behavior suggests the presence of pacemaker muscle fibers that oscillate. The onset is often associated with needle movement and the discharges start and stop abruptly. These potentials can occur in a variety of neuromuscular disorders and suggest that the animal has a chronic condition. Although these potentials were referred to as *pseudomyotonic potentials* at one time, they do not wax and wane in amplitude and frequency as do true myotonic potentials. From the loudspeaker of the electromyograph, these discharges have continuous high-pitched motor-like sounds.

Myotonic Discharges - *Myotonic potentials* occur in muscle as a result of abnormal permeability in muscle fiber membranes. Muscles continue to be electrically activated even after the cessation of volitional contraction. These high frequency (100 to 200/sec) potentials spontaneously wax and wane in amplitude and rate in an EMG pattern that has become the electrical signature of myotonia. In addition to normal presynaptic nerve activity, the onset may be precipitated mechanically such as with percussing the muscle or by EMG needle movement. Spontaneous activity may last for a second or more. In some types of myotonia, the repetitive discharges may be explained by altered chloride conductance in muscle membranes while in other types, the malady may be related to a disorder in sodium conductance. Audio monitoring of myotonic potentials reveal a

characteristic EMG sound, referred to as *dive-bomber potentials*.

### Evoked Activity in Muscle

Skeletal muscle activity is usually evoked by electrical stimulation of motor nerves with intramuscular needle or surface electrodes as recording electrodes. In other evoked responses, receptors are physiologically stimulated and muscles are reflexively activated. Muscle activity may also be produced by transcranial electrical or magnetic stimulation of the motor cortex.

### Compound Muscle Action Potentials

*Electrically Evoked* - When the motor nerve to a muscle is supramaximally stimulated with electrical current, motor units are activated as their nerve fibers reach threshold. When many fibers are simultaneously active, a *compound muscle action potential* (CMAP) can be recorded.

This potential is also referred to as the muscle response (**M response** or **M wave**). Depending on the specific muscle and recording electrodes, the amplitude of the M wave in dogs can range from a few to over a hundred millivolts (mV) and is proportional to the number and size of the discharging fibers. Figure 6 illustrates a latency period followed by the M wave in an interosseous muscle. The latency of the M wave is proportional to the distance between the muscle and the stimulating electrode location along the peripheral nerve. The duration is a reflection of synchrony, i.e., how closely muscle fibers discharge in time. For any given nerve, the further away from the muscle its motor nerve is stimulated, the longer the duration of the M wave and the lower the amplitude.

If a peripheral motor nerve is stimulated at two predetermined locations and CMAPs recorded for each stimulus, the **nerve conduction velocity** (NCV) can be calculated (Fig. 7).



Figure 6. Compound muscle action potential recorded from an interosseous muscle in response to an electrical pulse delivered to the ulnar nerve at the level of the radiocarpal joint. Horizontal division = 2.0 msec; vertical division = 2.5 mV. (Included with permission from: M. H. Sims. In: Electrodiagnostic evaluation. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994;

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Figure 7. Compound muscle action potentials (CMAPs) in the interosseous muscle of a dog as the result of stimulating the tibial nerve (*top*) and the sciatic nerve (*bottom*). The cross-hatches mark the beginning of the CMAP. The proximal latency was 8.0 msec, and the distal latency was 3.6 msec. The interelectrode distance was 296 mm, so the motor nerve conduction velocity was 67.3 m/sec (296

mm/8.0 msec - 3.6 msec). Horizontal bar = 2 msec; vertical division = 2.5 mV. (Included with permission from: M. H. Sims. In: Electrodiagnostic evaluation. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994; 349-368.). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Dividing the difference (in mm) between the proximal and distal stimulation sites by the difference (in msec) between proximal and distal CMAP latencies gives the NCV (in mm/msec or m/sec). Using this technique in dogs, NCV range from approximately 50 - 90 m/sec, depending on the peripheral nerve tested. In addition, cranial nerves can be evaluated with EMG techniques [24].

Normal values for NCV are age-dependent. Adult values for NCV are attained by approximately 6 - 9 months of age in dogs and begin to decline in dogs over approximately 8 years of age (Table 1). Each laboratory should establish that their normal values are in accord with values reported in the literature [20].

Table 1. Estimates of Motor Nerve Conduction Velocities (mean, meters per second) in Dogs and Cats at Different Ages				
	Sciatic-tibial Nerve		Ulnar Nerve	
Age	Dog	Cat	Dog	Cat
3 months	37	70	42	62
6 months	53	95	54	84

	Sciatic-tibial Nerve		Ulnar Nerve	
Age	Dog	Cat	Dog	Cat
1 - 8 years	62	95	63	87
9 years	57	94	52	77
10 years	58	94	51	97
14 years	48	80	51	78
16 years	39	---	37	---

Modified from: Swallow JS and Griffiths IR. [20] and Pillai et al. [34].

- For details, including mean and standard deviation values and ranges, consult the above references.
- Individuals should confirm these values in healthy animals in their own laboratories in order to establish their normal range.

When electrical current is applied to peripheral nerves, large nerve fibers reach threshold more easily than small fibers. The greater cross-sectional area of larger fibers offers less resistance to current flow than smaller fibers. In addition, large peripheral nerve fibers are capable of discharging at a faster rate than small fibers. Fiber size, myelination, and internodal distance are the key factors in determining conduction velocity—the larger the fiber, the faster the velocity. Nerve conduction velocity is always determined by the large fibers, even if there are fewer than normal present. For this reason, it is not unusual to find normal NCV during the early phases of demyelination, incomplete demyelination, or axonal degeneration. The distal stump of a completely transected axon will continue to conduct electrical impulses for a period of time that is roughly proportional to the distance between the injury and the muscle. During the interval of several days between damage and cessation of function, the CMAP duration will increase and the amplitude will decrease. The amplitude and duration of the CMAP may also be altered in any abnormality of the neuromuscular junction such as botulism. An extensive amount of data on CMAPs are available in the literature [1,6,13,21].

If a peripheral nerve is stimulated repetitively, the resultant CMAP will maintain its amplitude as long as the stimulation rate is not too high. In myasthenia gravis, a disease that affects the neuromuscular junction, the CMAP will show a decrement even at low rates of stimulation. The electrodiagnostic support for myasthenia gravis is a decrement in the CMAP of 10% or more using a stimulation rate of 2 - 3/sec.

When a peripheral nerve is stimulated electrically, nerve fibers conduct impulses in both directions from the point of stimulation. Orthodromic conduction in motor nerve fibers will produce a CMAP.

Antidromic conduction may re-excite the lower motor neuron. When this happens, a second volley of nerve impulses will produce a second smaller CMAP referred to as an **F response** or **F wave**. The latency of the F wave will depend upon the distance from the point of stimulation to the CNS and the distance from the participating LMN to the muscle. The F wave requires that the peripheral nerve proximal to the point of stimulation and ventral roots be functional. Analysis of the F wave can aid in the diagnosis of radiculopathy [25]. Various equations have been suggested to assess F waves, but the most straightforward method is to determine F wave latency with the stimulating needle at a standardized position and compare the latency to the normal range for dogs with similar limb length.

Central pathways that innervate lower motor neurons can be evaluated by stimulation of the motor cortex and recording *motor evoked potentials* (MEPs) from the spinal cord, peripheral nerves, or skeletal muscles. Direct stimulation has been accomplished with transcranial electrical current (Fig. 8) or electromagnetic pulses.

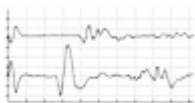


Figure 8. Transcranial motor evoked potentials recorded from the cranial tibial (*top*) and extensor carpi radialis (*bottom*) muscles in a dog in response to an electrical pulse delivered transcranially to the motor cortex. Each trace is an average of five responses. Horizontal division = 4 msec; vertical division = 1.2 mV. (Courtesy of G.M. Strain, Department of Veterinary Physiology, Pharmacology, and Toxicology,

College of Veterinary Medicine, Louisiana State University, Baton Rouge, LA.). (Included with permission from: M. H. Sims. In: *Electrodiagnostic evaluation*. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994; 349-368.). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Whereas the somatosensory evoked potential (see below) primarily monitors activity in the dorsal columns, MEPs utilize areas of the spinal cord that have a different blood supply. Cortical stimulation may cause bilateral responses in nerve and muscle, but the contralateral response has the lower threshold. Studies in animals and human beings have revealed that MEPs may be more sensitive than somatosensory potentials for assessing acute or chronic spinal cord injury.

**Reflexively Evoked Potential** - An electrical stimulus delivered to a peripheral nerve will excite sensory fibers, especially the large IA afferent fibers from muscle spindles. Impulses in these fibers monosynaptically excite the LMN, thus producing a second smaller CMAP which is called the **H reflex** or **H wave**. This is equivalent to elicitation of a myotatic reflex such as the patellar reflex. The latency of the H reflex is similar to the F wave but requires functional dorsal roots in addition to ventral roots and proximal peripheral nerve. By stimulating a peripheral nerve at two locations and dividing the interelectrode distance by the difference in H reflex latencies, one can calculate NCV of these fast-conducting sensory fibers. Because these proprioceptive fibers are as large (and sometimes larger) as the motor fibers innervating skeletal muscle, this type of sensory NCV will be in the same range as that in motor fibers. However, H waves are not reliably reproduced in all muscles, and their application to clinical veterinary electrodiagnostics remains limited at this time.

**Single-Fiber Potentials** - The discharge of a single muscle fiber is also of interest, especially in the diagnosis of junctionopathies. With a specially designed needle electrode, the electrical activity of single myofibers can be recorded as a part of a procedure called *single-fiber EMG* (SF-EMG). Single-fiber potentials are recorded and used to trigger the recording amplifier, or in some protocols, electrical stimuli are used as the trigger. When a fiber is found that is linked to a triggering event, then it is possible to measure its discharge time relative to the first potential (Fig. 9).

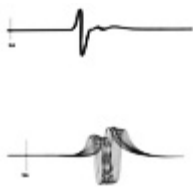


Figure 9. Sequential action potentials recorded from a single muscle fiber in response to an electrical axonal stimulation. Traces show normal latency variation or jitter (upper traces) and increased latency variation in a dog with myasthenia gravis (lower traces). (SA, stimulus artifact.) (From: Hopkins AL et al., [35]). (Included with permission from: M. H. Sims. In: Electrodiagnostic evaluation. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994; 349-368.). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Any variability in latency is called *jitter* and is due to a variation in synaptic delay between the end-plates. In some neuromuscular disorders, such as myasthenia gravis, the jitter value may increase or the second SF potential may be blocked altogether (Fig. 9). Although widely used in human electrodiagnostics, this technique is not frequently used in veterinary electrodiagnostics. A method has been reported in dogs in which electrical stimulation was substituted for the standard voluntary muscle activation used in the human patient.

## Electrical Activity in Peripheral Nerves

### Spontaneous Activity in Nerves

**Electroneurography** - This is the study of electrical activity in neural tissue such as peripheral nerve. When muscles contract volitionally, action potentials appear asynchronously in peripheral motor nerve fibers. This activity is mixed with action potentials in sensory neurons from peripheral receptors thus making it impossible to distinguish one type from the other. In addition, the action potential amplitudes are so low as to make a recording of this type of activity clinically impractical. Evoked activity in peripheral nerves, however, provides more usable information by synchronizing activity in either motor or sensory fibers.

### Evoked Activity in Nerves

Because peripheral nerve fibers conduct impulses bidirectionally, it would not be possible to simply stimulate a mixed nerve and record a compound nerve action potential that reflected activity in only sensory or motor fibers. For this reason, motor NCV is determined as described above. Sensory NCV, however, can be determined by stimulating a purely sensory nerve, or its cutaneous receptors, and recording from the parent nerve at a more proximal site or sites. Cutaneous areas exclusively innervated by nerves of interest are called *autonomous zones* and have been established for the major peripheral nerves in dogs. Sensory compound nerve action potentials (SNAP) are small and signal averaging is usually necessary. However, near field recordings are practical. With a needle recording electrode carefully placed adjacent to the superficial radial nerve, for instance, signal averaging is not required. As with other evoked potentials, amplitude and duration are important variables for interpretation. The measurement of sensory NCV provides objective data to explain loss of sensory or reflex function and to assist in the diagnosis of acquired or congenital sensory neuropathies. With the more recent availability of relatively inexpensive electrodes, microneurography will likely be adapted in veterinary medicine in the near future.

## Electrical Activity in the Central Nervous System

### Spontaneous Activity in the Brain

**Electroencephalography** - If electrodes are attached to the scalp overlying the cerebral hemispheres, activity in the brain can be recorded in awake, sedated or anesthetized animals. A record of this type of activity is called an **electroencephalogram** (EEG). The EEG provides important diagnostic information in certain neurological cases, and the reader is referred to the literature for more detailed information [5,8]. However, with the availability of newer imaging techniques such as computerized tomography, magnetic resonance imaging, and other types of scanning, the role of EEG is being revised such that EEG may not be included in the work up of many neurological cases. Rather, its importance may lie in work up of specific disorders such as epilepsy [26,27]. In a case where the scalp-recorded EEG was normal in a dog with intractable epilepsy, the electrocorticogram was recorded with electrodes implanted on the dura mater [37].

Visual interpretation of the EEG requires considerable expertise of the clinician, beyond what is needed for the training in other electrodiagnostic techniques. In addition to evaluating amplitude and frequency, the interpretation is based on evaluating factors such as symmetry, mental status, types and frequency of artifacts, identification of specific waveforms, and overall pattern. Some electroencephalographers record from awake animals, while others insist on tranquilization or anesthesia in order to reduce artifacts and to decrease the amount of preparation time. While it is true that sedatives and anesthetics alter normal patterns, some prefer these alterations to those produced by awake but uncooperative patients. The initial difference between the two techniques is seen in the low-voltage, short duration waves in the awake animal as a product of desynchronization. This is contrasted with higher voltage, longer duration synchronized wave characteristics of a sedated or asleep animal. The ability to evaluate both awake and drowsy pattern in an animal may provide a higher diagnostic yield.

A common recording technique consists of a montage of small needle electrodes placed subcutaneously in the scalp. Activities from preselected electrode pairs are fed to multiple amplifiers and printed on a strip-chart recorder. Although the time-favored approach to EEG analysis is the visual subjective method, computer-enhanced electroencephalographic recorders provide user-defined data analysis including power spectrum analysis and cortical mapping capabilities. Quantitative analysis of the EEG has been used in veterinary anesthesiology for purposes such as assessing depth of sedation [38,39].

Most abnormalities consist of high-voltage, high-frequency activity, high-voltage, slow-wave activity, spikes, spindles, or any combination of these. The first question answered by the EEG is whether abnormal activity is diffuse or focal. Focal abnormalities can be further defined by *triangulation*, a process that helps to localize the lesion. Commonly identified EEG abnormalities are the high-voltage, slow-wave patterns characteristic of hydrocephalus and the high-voltage, spiky waves associated with encephalitis.

### Evoked Activity in the Spinal Cord

**Spinal Cord Evoked Potentials** - Electrical stimulation of peripheral nerves will result in recordable volleys of activity in the spinal cord [28]. These complex potentials, referred to as *spinal cord evoked potentials* (SCEP), are usually polyphasic and tend to undergo temporal dispersion as recording electrodes are located more rostrally (Fig. 10).

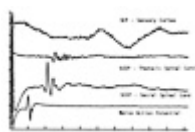


Figure 10. Evoked potentials recorded from (top to bottom) cortex, thoracic spinal cord, sacral spinal cord, and peripheral nerve in a dog as a result of electrical pulses applied to the tibial nerve. Horizontal division = 5 msec; vertical division = 5  $\mu$ V for nerve action potential, 2.5  $\mu$ V for both spinal cord evoked potentials (SCEP), and 1.25  $\mu$ V for the somatosensory evokes potential (SEP) from the cortex. (Included with permission from: M. H. Sims. In: *Electrodiagnostic evaluation*. K.G. Braund, 2nd ed. Clinical

syndromes in veterinary neurology. St Louis: Mosby, 1994; 349-368.). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Cord dorsum potentials can be recorded percutaneously from the lumbar enlargement after stimulation of nerves in the pelvic limb or tail and from the cervical enlargement after forelimb nerve stimulation. Conduction times and conduction velocities can be calculated for spinal cord tracts in the same way as peripheral nerves. SCEPs are particularly indicated for determining the location and severity of spinal cord lesions or lesions affecting the dorsal roots [29]. However, SCEP should not be used for determining prognosis, especially if only measured on one occasion. For instance, in dogs with herniated intervertebral disks, the SCEP may be absent initially and later return as the animal recovers.

### Evoked Activity in the Brain

**Brainstem Auditory Evoked Responses** - Electrical potentials that are produced in response to auditory stimulation are called

*auditory evoked responses* (AER). One of the principle means for assessing auditory function in animals is the *brainstem auditory evoked response* (BAER). Short-duration auditory stimuli in the form of clicks are delivered to the external auditory canal and signal-averaged responses are recorded from subcutaneous scalp electrodes. In small animals, BAER occur within the first 10 msec after stimulus application and consist of 6 - 7 waves with amplitudes in the microvolt or submicrovolt range (Fig. 11).

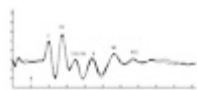


Figure 11. Brain stem auditory evoked response (BAER) in response to clicks (intensity = 90 dB nHL) delivered at a rate of 11.4/sec. Each trace is an average of responses to 1000 clicks alternating between condensation and rarefaction. Roman numerals identify positive BAER peaks. Horizontal division = 1 msec; vertical division = 0.61  $\mu$ V. (Included with permission from: M. H. Sims. In: *Electrodiagnostic evaluation*. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994; 349-368.). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Generally, the peaks of the BAER are produced by the auditory nerve and brainstem portions of the auditory pathway, but individual peaks cannot be correlated with specific nuclei in the auditory pathway. As with most of the electrodiagnostic tests, the responses change during maturation and in geriatric animals compared to the normal adult. The clinician must be aware of the age at which responses attain normal adult values and use age-appropriate comparisons [30]. In cases of severe cochlear damage or hereditary agenesis, a flat-line recording may result (Fig. 12). This is a common finding in a large number of breeds of dogs with hereditary deafness and forms the basis for screening for inherited deafness in litters of puppies of certain breeds around 5 weeks of age. Based on behavior alone, deafness may be suspected in puppies or adult dogs. However, the BAER is an objective method for confirming partial or total deafness, and for identifying animals that are unilaterally deaf. In dogs with suspected brainstem disorders, BAER may also be used to assess lesions in the brainstem that do not necessarily affect hearing. Poncelet et al reported a method for estimating audiograms from brainstem tone-evoked potentials in puppies [40].

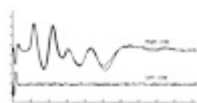


Figure 12. Brain stem auditory evoked responses recorded from the left side (bottom trace) and right side (top trace) of a dog with a hereditary cochlear dysfunction on the left side. Each trace is an average of 1000 responses to click stimuli at an intensity of 90 dB nHL and a rate of 11.7/sec. Horizontal division = 1 msec; vertical division = 0.61  $\mu$ V. (Included with permission from: M. H. Sims. In: *Electrodiagnostic evaluation*. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994; 349-368.). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Middle and Late Latency Auditory Evoked Responses - In contrast to the short-latency response described above, extending the analysis time on the amplifier will produce AER that occur later and more rostrally in the neuroaxis. Middle-latency AER components occur at a latency of 10 - 50 msec (Fig. 13) and *late-latency* AER are found in the 50 - 250 msec range. These potentials are not as clearly defined as the short-latency BAER, and therefore have not been used as extensively in veterinary medicine, although their implications for the examination of dogs with neurological disorders is being studied [31].



Figure 13. A middle-latency auditory evoked response in a cat in response to clicks at an intensity of 90 dB nHL at a rate of 4.7/sec. Components of the middle latency response are labeled Po, Na, Pa, Nb, and Pb. The peak labeled V is wave V of the brain stem auditory evoked response. Each trace is an average of responses to 2000 stimuli. Horizontal division = 6 msec; vertical division = 0.762  $\mu$ V. (From Sims MH [36]). (Included with permission from: M. H. Sims. In: *Electrodiagnostic evaluation*. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994; 349-368.). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Somatosensory Evoked Potentials - When sensory receptors are stimulated at specific locations in the body (soma), the arrival of impulses in the somatosensory cortex can be monitored with strategically placed electrodes. These complex potentials are called *somatosensory evoked potentials* (SEPs). Some authors refer to these as *cortical potentials* or *cortical evoked potentials* because components of the waveform are believed to arise from the cortex. Many SEPs are initiated by the electrical stimulation of mixed peripheral nerves (Fig. 14). With multi-channel recording, ascending volleys can be tracked at different levels in the periphery and CNS to provide information about lesion localization (Fig. 10). Miko et al. recently reported on the use of recording electrodes placed in the nasopharynx and trachea, with stimulation of the median nerve. They concluded that potentials recorded with nasopharyngeal and tracheal electrodes are suitable for intraoperative neurophysiologic monitoring in anesthetized dogs [41].

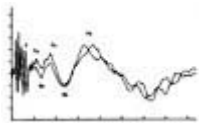


Figure 14. Somatosensory evoked potential recorded from a cat in response to stimulation of the right tibial nerve at a rate of 2.7/sec. Electrodes were placed on the midline over the occipital protuberance (positive) and on the midline over the cranial border of the frontal sinuses (negative). Each trace is an average of 256 responses. Small and large peaks are labeled p or P (positive) and n or N (negative), respectively. Horizontal division = 25 msec; vertical division = 1.22  $\mu$ V. (Included with permission from: M. H. Sims. In: *Electrodiagnostic evaluation*. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994; 349-368.). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

**Visual Evoked Potentials** - A variety of light stimuli will produce cortical responses that are referred to as *visual evoked potentials* (VEPs). Stroboscopic flashes and light-emitting diodes have been used to record VEPs in cats and dogs (Fig. 15). These cortical potentials are important in distinguishing between visual problems that originate in the eye and those that are due to lesions in the visual pathway distal to the eye. The clinician should be aware that the VEP tends to be contaminated by the electroretinogram, the waves of which can be recognized by their early latencies or by simultaneous recording of VEP and ERG (see below).

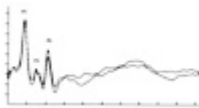


Figure 15. Visual evoked potential (VEP) recorded from a dog in response to stimulation with a 3 x 5 matrix of light-emitting diodes. Major peaks of the VEP are labeled P1, P2, and P3. Each trace is an average of 256 responses. Horizontal division = 25 msec; vertical division = 0.6  $\mu$ V. (Included with permission from: M. H. Sims. In: *Electrodiagnostic evaluation*. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994; 349-368.). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

## Evoked Activity in the Retina

### Flash Electroretinogram

**The Electroretinogram (ERG)** - The Electroretinogram is a complex response of the retina to light stimulation. A contact lens electrode is often referenced to a subcutaneous electrode placed posterior to the lateral canthus. Subconjunctival needle electrodes and palpebral electrodes do not provide responses of as high quality as obtained with contact lens electrodes. The most commonly used means of stimulation is a white stroboscopic flash and the resultant activity is called a *flash ERG* or *FERG*. Guidelines for clinical ERG in dogs were presented at the 1st European Conference on Veterinary Visual Electrophysiology [42]. The FERG has been used extensively in veterinary medicine for assessing general function of the retina (Fig. 16) and as a screening procedure for retinal function prior to cataract surgery. Higher stimulation rates and color filters have been used to distinguish between rod and cone function. The canine FERG may have amplitudes up to 350  $\mu$ V and may require a time base of 600 msec to present its complete waveform. The reader should consult reviews [32,43] and texts of veterinary ophthalmology for more detailed information on ERG.

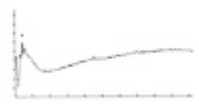


Figure 16. Flash electroretinogram recorded from a dog in response to a white stroboscopic flash delivered to one eye. The a and b waves are labeled. Horizontal division = 60 msec; vertical division = 48.8  $\mu$ V. (Included with permission from: M. H. Sims. In: *Electrodiagnostic evaluation*. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994; 349-368.). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

**Oscillatory Potentials** - *Oscillatory potentials* (OPs) are small wavelets appearing on the ascending and descending slopes of the b-wave of the ERG (Fig. 17). Filter settings can be varied to enhance or eliminate the OPs. The OPs are thought to arise from negative feedback circuits in the retina with major contributions from the amacrine cells. Because OPs are sensitive to changes in retinal blood supply, these potentials have been used to assess visual disorders caused by circulatory dysfunction. Possible applications in veterinary medicine include evaluation of diabetic retinopathies or elevated intraocular pressures caused by glaucoma.

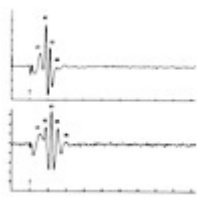


Figure 17. Oscillatory potentials recorded from a cat (*top*) and a dog (*bottom*) in a response to a single white stroboscopic flash after dark adaption. Frequency bandpass = 100 to 500 Hz. Positive peaks are labeled 01 through 04 or 05 for the cat and dog, respectively. Horizontal division = 25 msec; vertical division = 12.2  $\mu$ V (*top*) and 9.76  $\mu$ V (*bottom*). (*Arrow*, flash discharge). (Included with permission from: M. H. Sims. In: *Electrodiagnostic evaluation*. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994; 349-368.). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

**Pattern Electoretinogram** - The use of a more complex visual stimulus, such as alternating patterns of light and dark bars, will produce an ERG that is called a *pattern ERG* or *PERG* (Fig. 18).

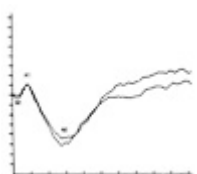


Figure 18. Pattern electroretinogram (PERG) recorded from a dog in response to visual stimulation with a vertical grating pattern at a spatial frequency of 0.06 cycles per degree of visual angle. Each trace is an average of 512 responses. Negative (N) and positive (P) peaks are labeled for the major PERG peaks. Traces are replicates. Horizontal division = 50 msec; vertical division = 0.61  $\mu$ V. (Included with permission from: M. H. Sims. In: *Electrodiagnostic evaluation*. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994; 349-368.). - To view this image in full size go to the

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The waveform of this complex potential has some resemblance to the FERG. However, whereas the FERG is a diffuse response of retinal photoreceptors to light, the PERG is thought to arise from more proximal portions of the retina such as ganglion cells. The PERG has been evaluated as an indicator of increased intraocular pressure in dogs [33].

Manuscript adapted from: M. H. Sims. In: *Electrodiagnostic evaluation*. K.G. Braund, 2nd ed. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994; 349-368.

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## Cerebrospinal Fluid (22-Aug-2003)

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### Introduction

The presence of cerebrospinal fluid (CSF) within the cavities of the brain was already known to the ancients. Probably, the first report of the existence of CSF was performed in the 17th century B.C., and Hippocrates described the occurrence of fluid in brain cavities in the 4th century B.C.; however, it was thought to be pathological. Galen described the ventricular cavities in the 2nd century A.D. For a long time these cavities were thought to be filled with "vital spirit". Only in the 16th century A.D. did Vesalius again discover a watery humor. Systematic studies of this fluid started later and in 1825 Magendie performed the first tap of the cisterna magna in animals. The examination of CSF was introduced by Quincke 1891, and in 1901 cytological techniques were established by Widal and others [1].

### CSF and the Ventricular System

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### Cerebrospinal Fluid and the Ventricular System

#### Anatomy

Cerebrospinal fluid is mostly located in the ventricular system and the subarachnoid space. The **ventricular system** develops from the neural tube and includes the lateral ventricles, third ventricle, the mesencephalic aqueduct and the fourth ventricle, which continues into the central canal of the spinal cord. The cranial cavity is a closed space and requires a continuous adjustment of the intracranial pressure. In the cavity the volumes responsible for this pressure are the brain parenchyma, the CSF and the blood [1,2].

In part the CSF is produced by the **choroid plexus** which includes the choroidal epithelium, blood vessels and interstitial connective tissue. This plexus is formed as a result of the invagination of the ependyma into the ventricular cavities by blood vessels of the pia mater. The epithelium of the plexus is continued by the ependymal lining of the ventricles. The choroid plexus has an extensive blood supply that reflects its active metabolic activity. In addition, there exists a nerve supply, an extensive perivascular autonomic innervation derived in part from the sympathetic and the vagal nuclei. There is much evidence for adrenergic, cholinergic and peptidergic innervation. The choroidal epithelium is composed of a single row of epithelial cells, arranged in villi around a core of blood vessels and connective tissue. Numerous infoldings and microvilli provide a structure which resembles other epithelia noted for fluid transport. A membranous barrier to the movement of macromolecules are the tight junctions, which join adjacent choroidal epithelial cells. Tight junctions also characterize brain endothelial cells and the cells of the arachnoid membrane. The electrical resistance found on the apical surface of the choroidal epithelium has also been attributed to these tight junctions [1].

**Brain capillaries** have a special morphology in comparison to capillaries of other organs. Endothelial cells in brain capillaries are joined by tight junctions, which results in a continuous layer of cells separating blood from extracellular fluid of the brain. Also, the surface of the vessels have high electrical resistance, which is thought to be an additional function of the tight junctions. Since these junctions serve as a barrier to the movement of ions and molecules the transport is performed by endothelial cells. In addition brain capillaries are surrounded by a basement membrane, approximately 25% the width of endothelial cells [1]. The function of this membrane is to maintain the integrity of the capillary tube under adverse conditions such as osmotic changes or increased hydrostatic pressure from sudden elevations in the blood flow. The capillaries are surrounded by different cell types, pericytes, perivascular macrophages and astrocytic end-feet.

The cerebral ventricles are lined with a layer of **ependymal cells** followed usually by a subependymal layer of glial fibers and glial cells. At this location an exchange between ventricular fluid and the adjacent subependymal extracellular fluid of the brain occurs.

The brain and the spinal cord are surrounded by the **leptomeninges**. They are divided into the arachnoid mater and the inner layer, the pia mater. The two membranes contain the subarachnoid space filled with the extraventricular CSF. The leptomeninges contain few capillaries. The pia mater forms the outer surface of the perivascular space through "invagination" into the nervous system and tissue derived from the arachnoidea contributes to the inner wall of this space. Filaments of spinal and cranial nerves are surrounded in a similar way by a reticular (endoneurial) sheath derived from the pia. The pia mater is also involved in the formation of the ventricles (e.g., roof of the 3rd ventricle and in part of the 4th ventricle). The perivascular space of Virchow-Robin extends from the subarachnoid space to a variable depth within the brain [2].

The **extracellular interstitial fluid** of the brain is thought to have a volume in the range of 15 to 20%. The space is greater in gray matter than in white matter, the former having a higher water content than the latter.

The **dura mater** is a thick and inelastic membrane which encompasses the brain, spinal cord and lumbar sac. The meningeal layer is the protective envelope of the brain. The falx, the tentorium and the diaphragma of the sella are formed by reduplication of the inner meningeal layer of the dura. The dura has an extensive lymphatic supply and a parasympathetic and sympathetic innervation system. The dura is outside the blood-brain barrier.

A connection exists between the **scala tympani** and the subarachnoid space by the cochlear aqueduct. The pressure in the three compartments of the cochlea shows changes parallel to those recorded in the CSF in several animal species. However, the actual rate of flow between the CSF and the perilymph via the cochlear aqueduct is not exactly known. It is possible that the endolymph duct may be important in the spread of infection between the inner ear and the meninges [1].

## Physiology

### Secretion

CSF is produced by a number of sites. Beside the secretion of CSF by the choroid plexus the fluid derives also directly from the brain by the ependymal lining of the ventricular system and the pia-glial membrane and from blood vessels in the pia-arachnoid. The rate of CSF formation in various species varies between 0.2 and 0.5 ml/minute/gm choroid plexus. In the dog the formation rate is approximately 0.047 ml/minute (dependent on the size of the animal), in the cat 0.017 ml/minute, in the rat 0.002 ml/minute and in man 0.35 ml/minute [1-3]. CSF is produced by ultrafiltration from blood plasma and by active transport mechanisms. Hydrostatic pressure in the capillaries initiates the transfer of water and ions to the interstitium and then to the choroidal epithelium. The further transport occurs across tight apical junctions and through cells. Both transmembranal transfers are probably dependent upon ion pumps and are directly related to sodium transport, which depends upon the membrane-bound enzyme sodium-potassium activated ATPase present at the apical surface as well as at the intercellular clefts. A further important enzyme is carbonic anhydrase. The sodium content of plasma and CSF is about the same; however, CSF has an excess of chloride and magnesium and a deficit of potassium and bicarbonate. A further difference is seen in the water content. Plasma is 93% water, CSF 99% [1]. The fact that the concentration ratios of the major ions in CSF are different from those in a protein-free filtrate indicates that the composition of the CSF depends upon secretory processes. Further specific mechanisms such as facilitated diffusion into the CSF exist for the membrane transport of vitamins, nucleosides, purines, glucose and amino acids essential for brain development and metabolism, whereas toxic metabolites are cleared from CSF to plasma. It was shown that the rate of CSF production is independent of moderate variation in the level of intraventricular pressure of short duration. However, in studies with chronically hydrocephalic animals a reduction in CSF formation is observed with increasing pressure. In contrast, acute changes in blood osmolality alter the CSF production, but it is suspected that the choroid plexus will adapt to chronic osmotic derangement, so that any changes in function would be transient. In addition the choroid plexus serves as an "ectopic renal tubular epithelium" in clearing the CSF from toxic metabolites.

### Absorption

The CSF circulates from the ventricular system to the subarachnoid space. Along the spinal cord and the central canal in animals a caudal flow, as well as a circulating one exists. In humans besides this caudal flow the CSF has the tendency to

flow also cranially. The cranial cavity is a closed space and in the equilibrium state the rate of absorption of CSF equals its rate of formation. The arachnoid villi are the major place for CSF absorption [2,3]. The mechanism for the bulk flow reabsorption into the venous system depends upon the hydrostatic pressure within the subarachnoid space. Other sites are the choroid plexus, diffusion into brain and capillaries, veins and lymphatics placed around spinal nerve roots.

### **Function**

The CSF has several functions, such as physical support, excretory function, intracerebral transport and control of the chemical environment of the central nervous system (CNS). The CSF helps in the protection of the brain from acute blood pressure changes and, therefore, in the regulation of intracranial pressure. Since the CSF is considered to be an intracerebral transport medium, the fluid is also useful for clinical research.

### **Composition**

As already described, the CSF is a watery solution containing ions and different substances to serve as an intracerebral transport medium for nutrients, neuroendocrine substances and neurotransmitters. Despite the different composition in relation to plasma, the osmolality of the two fluids remains the same (289 mOsm/L) [1]. In comparison to plasma, glucose is slightly diminished in the CSF (about 80%) and there is much less protein, which is mostly albumin. In the normal dog the protein content is less than 25 mg/dl. In addition to these substances a few leukocytes are seen in the CSF, since the CNS is constantly screened by the immune system. In the CSF of normal dogs, 0 - 3 cells/ $\mu$ l, mostly lymphocytes, are counted.

### **Acquisition (techniques of CSF Tap)**

In clinics the CSF is analyzed for its cellular and chemical constituents. CSF is obtained by cisternal puncture in lateral recumbency during general anesthesia. After surgical preparation the puncture of the cerebellomedullary cistern is performed between the occipital bone and the atlas using 22 gauge, 1.5-inch spinal needles with a stylet. For the procedure, the head is held at a right angle to the vertebral column. Avoid excessive flexion of the head since it might occlude the airway. The animal has to be observed for adequate ventilation during the whole procedure. The landmark is a triangle composed from the occipital protuberance and the wings of the atlas. The puncture follows in the middle of this triangle. In animals which are not heavily muscled the space between the occipital bone and the arch of the atlas can be palpated. The needle is carefully inserted, the puncture of the dura mater and atlantooccipital membrane is felt, sometimes a slight muscle twitching occurs, when the needle is in the right place. When the stylet is removed, CSF flow is observed, which is the only reliable sign of a successful puncture. The CSF is collected in a sterile tube. The pressure can be measured using a spinal manometer [4,5], but the additional information is minimal. Therefore, most examiners do not recommend the additional manipulation. The amount of CSF, which can be obtained per animal, is 1 ml / 5 kg. Mostly, 1 - 2 ml are taken and sufficient for the most important examinations. If only a few drops can be obtained, the measurement of the protein content and the cell count is feasible with only 100 - 200  $\mu$ l CSF. By puncture of radicular vessels blood contamination might occur.

Another technique to obtain a CSF sample is the lumbar puncture (L5-L6). CSF can be taken in most cats with this procedure, although in dogs the technique is more difficult. Sometimes only a few drops are obtained and blood contamination occurs more frequently than with the suboccipital puncture. In addition, in normal CSF the number of cells counted after lumbar puncture is somewhat higher.

Cerebrospinal fluid pressure in the subarachnoid space can be measured after the puncture. Values of both the cervical and lumbar spines are affected by changes in body position. Pressure is reduced by inclining the body position to 30, 60 and 90 degrees [6].

### **Normal and Pathological Findings**

#### **Color**

The CSF is a watery, clear and colorless fluid. Every change from this waterlike appearance is abnormal. The CSF is cloudy when a high amount of cells are present ( $> 500/\mu$ l). A high protein content can enhance this turbidity and produces a more viscous fluid. Red color is indicative of hemorrhage, in most cases caused by puncture of radicular vessels. If the CSF clears after centrifugation, the coloration was caused by a traumatic tap. However, a red or yellow staining after centrifugation is indicative for a pathologic hemorrhage, since the erythrocytes degenerate easily in the CSF. Xanthochromia, a yellow color of the CSF, is typical for subarachnoid hemorrhage in the absence of hyperbilirubinemia. It is caused by an accumulation of blood pigments and occurs several hours after the hemorrhagic insult (bleeding after trauma, in arteritis cases or other severe CNS inflammation, as well as in vascular or bleeding disorders).

#### **Cell Counts**

The cerebrospinal fluid and its cells are a valuable source of information for diagnostics and research since they reflect, at least in part, the immune response occurring in the CNS. The examination of CSF cells is especially useful in cases in which

an ongoing inflammatory reaction is suspected (inflammatory/infectious diseases of the CNS, tumors). The total number of cells is determined by use of a cell counting chamber: mostly the Fuchs-Rosenthal chamber is used. The counting should be performed within about 30 minutes after CSF collection, since the cells degrade rapidly in a fluid with low protein content. In particular, granulocytes are very sensitive and are lysed up to 40% after 2 hours at room temperature. Refrigerating helps to minimize the degeneration [7]. In the CSF of normal dogs and cats 0 - 3 cells/ $\mu$ l are counted, mostly mononuclear cells (lymphocytes and monocytes). It should be reminded that a normal cell count of 3 leukocytes/ $\mu$ l CSF is equivalent to 3000 white blood cells/ml. Slight contamination with erythrocytes because of a traumatic puncture does not severely effect the counting results. Approximately one white blood cell is subtracted from the CSF leukocyte count for every 500 - 700 erythrocytes present.

In cases with severe anemia or leukocytosis the following formula may be used to correct the leukocyte count in the CSF:

$$W = WBC_F - \frac{WBC_B \times RBC_F}{RBC_B}$$

W = actual or calculated leukocyte content of CSF;

WBC<sub>F</sub> and WBC<sub>B</sub> = counted white blood cells in the CSF and blood;

RBC<sub>F</sub> and RBC<sub>B</sub> are the numbers of erythrocytes/ $\mu$ l in CSF and blood [1].

In the author's experience these calculations are probably unnecessary and do not improve the clinical diagnosis in that they do not influence the degree of pleocytosis.

In case of a pleocytosis, an increased cell count, which is graded as mild (5 - 50 cells), moderate (50 - 200 cells) or marked (> 200 cells), a differential cell count is performed as soon as possible. Enumeration and identification of the cells helps to narrow the clinical differential diagnosis [8,9]. For closer evaluation of the CSF cells cytopspin preparations are commonly used [10]. The cytocentrifuge accumulates all the cells in a volume of 0.5 to 1.0 ml of CSF. In case of a marked pleocytosis, 200  $\mu$ l is sufficient for a differential cell count. Thus, cytocentrifugation can prepare about 300 times more cells for evaluation than observed in the counting chamber. A sedimentation chamber can also give nice results. To prevent rapid cell degeneration during the time of the laboratory procedure and to obtain good cytopspin preparations protein has to be added to the CSF sample (about 1/3 of a 10% bovine serum albumin solution and 2/3 of CSF). CSF samples with a high protein content are centrifuged without addition of albumin. A darkly stained background complicates the evaluation of the cells. After staining (DiffQuick, Papanicolaou) the percentage of lymphocytes, plasma cells, monocytes, macrophages, neutrophils and eosinophils is counted, the cells are evaluated by their size and appearance and mitosis or tumor cells are searched for [10]. Pleocytosis with predominantly lymphocytes and plasma cells is found in viral infections and during the chronic phase of steroid responsive meningitis-arteriitis (SRMA) [11], in granulomatous meningoencephalomyelitis (GME) and in breed-specific necrotizing encephalitis. A predominantly neutrophilic pleocytosis is characteristic for bacterial infections and the acute stage of SRMA [11]. A mixed cell population is frequently seen in protozoal diseases, FIP, in chronic bacterial infections, in necrotic lesions and in GME [12]. Eosinophils are found in the rare eosinophilic encephalitis of unknown origin, in protozoal, parasitic and mycotic infections, but also occasionally in GME, FIP and certain tumor types (e.g., histiocytosis) [13]. Tumors mostly have an unspecific differential cell count. In lymphosarcoma large uniform lymphoid cells are characteristic and mixed with a "normal" lymphocyte population. In meningioma a neutrophilic pleocytosis might occur. The differential cell count is only helpful in combination with the clinical examination, signalment, history and further testing (blood, imaging etc.) to establish a clinical diagnosis. Because of this limitation, the evaluation of changes in lymphocyte subpopulations of CSF cells in neurologic diseases might be helpful to further characterize a disease *in vivo*. Therefore, normal control data for the dog were established using flow cytometry and immunocytochemistry [14,15]. It could be shown that lymphocyte populations in CSF differ from peripheral blood in a few subsets. A relatively high degree of individual variation was found, not only in dogs of different breeds and ages, but also in an inbred Beagle population. These large individual variations suggest that only repeated paired CSF-blood samples taken during the course of the neurologic disease within the same individual would provide meaningful results. CD3+ and CD4+ T-cells were significantly lower in normal CSF. Of great interest is the fact that T-cells, characterized by double staining CD3/CD45RA are present in variable numbers in normal CSF. In other species they are known to be naive or resting T-cells. CD4/CD45RA positive cells seem to be an important subpopulation of these CD45RA positive T-cells underlining the fact that the CNS is constantly observed and screened by the immune system. However, systematic flow cytometry analysis of CSF is feasible in larger animals such as dogs [14]. Occasionally bone marrow contamination of CSF might occur after lumbar puncture [16].

## Glucose

The CSF glucose is dependent upon blood glucose level and the rate of metabolism in the CNS. There are two mechanisms

responsible for the entry of glucose into the CSF: carrier mediated diffusion (glucose transporter protein) and simple diffusion. A variable time is required before CSF glucose level reaches an equilibrium with blood glucose (2 - 4 hours) [1]. In general the CSF glucose level is a complex function of the blood glucose level during the previous 4 hours. CSF levels are usually 60 - 80% of blood levels. CSF and blood glucose levels should be obtained simultaneously. An increase in the CSF glucose level is not diagnostically important and reflects hyperglycemia within 4 hours prior to the puncture. Decreased CSF glucose levels were associated with bacterial and fungal meningitis, in which microorganisms and polymorphonuclear leukocytes utilize glucose. However, in the dog, bacterial meningitis is a rare finding in comparison to steroid responsive meningitis-arteriitis. In the later disease extremely high numbers of neutrophils may be found (up to 2000 cells/ $\mu$ l). In this disease low glucose levels are measured despite the fact that no infectious agent has been found to date. Neutrophils are supposed to have an increased glycolysis, particularly when these cells are active (phagocytosis, production of oxygen radicals etc.). Low glucose levels were also reported in diffuse meningeal neoplasia and are therefore not considered anymore to be of specific diagnostic value. In summary, low CSF glucose levels in the absence of hypoglycemia indicate the presence of a diffuse meningeal disorder.

### **Protein**

In contrast to glucose levels, the measurement of protein levels in the CSF is important in the quest to obtain a differential diagnosis. Most proteins normally present in the CSF are derived from blood. In the dog and cat, normal CSF protein levels after suboccipital puncture are usually less than 25 mg/dl and might be somewhat higher in lumbar puncture samples. The kinetics of protein exchanges were studied with labeled albumin. Following intravenous injection, it needed 20 hours for albumin to reach equilibrium levels in the CSF of dogs. Protein entry depends chiefly upon pinocytosis across capillary endothelial cells, but also upon the isoelectric point. It is considered that more processes are involved than restricted filtration. The exit rate of protein from the CSF to blood is about 200 times the entry rate and normally is performed by passage across the arachnoid villi into the venous blood, presumably by macrovesicular transport. Qualitative measurement of the protein level is performed with the Pandy solution, a 10% carbolic acid solution, which precipitates globulin. Normal CSF samples do not show any turbidity after being added to the Pandy solution. Depending on the protein level a recognized turbidity is specified as 1+ to 4+ positivity. The biuret method, normally used for quantification, is not sensitive enough to measure CSF protein levels. Several methods for quantitative measurement of CSF protein level were adapted for use in animals, such as turbidometric methods using trichloroacetic acid, benzethonium chloride in an alkaline environment or nephelometry. An increased protein content serves as a nonspecific indicator of CNS disease and may be caused by a damaged blood-brain barrier or an increased local IgG production within the CNS. Elevated protein levels are therefore found in inflammatory/infectious, toxic/metabolic, vascular and neoplastic diseases.

### **IgG-Index**

Measuring the IgG-index, which is a calculated quotient using IgG and albumin content of cerebrospinal fluid and serum to detect intrathecal IgG-synthesis, can distinguish inflammatory/infectious diseases of the CNS from other disorders [17].

$$\frac{\text{IgG}_{\text{CSF}} / \text{IgG}_{\text{serum}}}{\text{Albumin}_{\text{CSF}} / \text{Albumin}_{\text{serum}}}$$

In most dogs with infectious/inflammatory diseases, with the exception of the acute form of nervous canine distemper, an elevation in the IgG-index can be determined. Tumors of the CNS, where pleocytosis can be detected, have an IgG-index within the normal range with an exception of lymphoid tumors and meningiomas with secondary cellular infiltration. The demonstration of intrathecal immunoglobulin synthesis resulting from infiltration of IgG-producing lymphocytes inside brain and spinal cord is a specific indication for the presence of inflammation in the CNS. Intrathecal IgG-synthesis can be shown by comparing the amount of immunoglobulin in the CSF with that in serum using albumin as a reference protein. Albumin can cross the blood-brain barrier, but in contrast to IgG, cannot be produced in the CNS itself. Several methods have been used for quantitation of these proteins in animal CSF, such as rocket immunoelectrophoresis, single radial immunodiffusion, agarose electrophoresis, ELISA and laser nephelometry.

Another immunoglobulin that can be measured in the CSF by ELISA is IgA [18,19]. A combined elevation of CSF and serum IgA levels is highly indicative for steroid responsive meningitis-arteriitis [11]. A single elevation of IgA in the CSF is only indicative of a primary (inflammatory/infectious disease) or secondary immune reaction (e.g., neoplasia). Various electrophoretic techniques were also applied in animals but did not enhance the diagnostic value of the CSF examination [20,21]. Other proteins were measured such as the myelin basic protein [22], S-100 protein and the C-reactive protein to narrow the clinical diagnosis to demyelination or to distinguish bacterial from viral meningoencephalitis [1,23]. However, the measurement of these proteins remains of theoretical interest and is not useful in clinical practice since too many disorders

are accompanied by an elevation of these proteins.

<b>Table 1. Summary of Most Important CSF Findings in Different CNS Diseases</b>			
<b>Disease</b>	<b>Protein Content</b>	<b>Cell Count</b>	<b>Dominant Cell Type</b>
Non-inflammatory distemper	Normal - slightly elevated	Normal, mild pleocytosis (rare)	Mononuclear cells
Inflammatory distemper	Slightly - strongly elevated	Mild - moderate pleocytosis	Mononuclear cells
Other viral diseases	Slightly - strongly elevated	Mild - moderate pleocytosis	Mononuclear cells
Bacterial encephalitis	Slightly - strongly elevated	Moderate - marked pleocytosis	Predominantly neutrophils
Protozoal encephalitis	Slightly - strongly elevated	Moderate pleocytosis	Mixed population, sometimes eosinophils
Fungal encephalitis	Strongly elevated	Moderate - marked pleocytosis	Mixed population, sometimes eosinophils
Parasitic infection	Slightly - strongly elevated	Mild - moderate pleocytosis	Mixed population, sometimes eosinophils
Granulomatous meningoencephalo-myelitis	Slightly - strongly elevated	Moderate - marked pleocytosis	Varying: mononuclear cells, mixed population, occasionally eosinophils
Steroid-responsive meningitis-arteriitis	Slightly - strongly elevated	Marked pleocytosis	Acute: neutrophils; Protracted: mononuclear cells
Breed specific necrotizing encephalitis	Slightly elevated	Mild - moderate pleocytosis	Mononuclear cells
Feline Infectious Peritonitis	Strongly elevated	Marked pleocytosis	Mixed population, occasionally eosinophils
Eosinophilic encephalitis	Slightly - strongly elevated	Mild - moderate pleocytosis	Eosinophils
Neoplasia	Varying: normal - strongly elevated	Varying: normal - marked pleocytosis	Varying: mononuclear cells, neutrophils (e.g., meningioma), occasionally eosinophils and tumor cells
Necrotic lesions (different causes)	Normal - slightly elevated	Varying: normal - marked pleocytosis	Mixed population
Degenerative lesions	Normal - slightly elevated	normal	---

### Antigen Detection

The IgG-index is a valuable tool to diagnose an inflammatory/infectious disease. The differential cell count together with the signalment, history and additional examinations such as blood values can give a hint as to the etiology of this group of diseases. However, to prove the etiology of an inflammatory/infectious disease, antigen detection is necessary. Occasionally bacterial or fungal organisms may be seen by microscopic evaluation, especially *Cryptococcus neoformans* [24]. However, it must be determined if the microorganisms are a contamination of the CSF after the puncture or are the causative agent of a bacterial encephalitis. If bacteria contaminate collecting tubes or slides for cytospins, neutrophils are still able to phagocytose. Therefore intracellular bacteria are not proof of a causative agent for an encephalitis. If bacterial encephalitis is



suspected, the CSF should be cultured and growing bacteria have to be classified. In most cases of bacterial meningoencephalomyelitis, microorganisms are either not present in the CSF or only present in low numbers. Culture results can be negative. PCR techniques are evaluated to improve the diagnostic work-up. In cases of suspected viral encephalitis, such as canine distemper encephalitis, virus detection is performed either by staining techniques (e.g., indirect immunofluorescent antibody examination) or by PCR [25]. Specific antibodies can be found in the CSF [26,27]; however, they are not diagnostic [28,2]. Serial serum determinations are necessary for the determination of a causative agent or the evaluation of specific indices [30]. For the latter, no experience exists yet in small animal medicine.

### **Enzymes**

A wide variety of assays to measure enzymes in serum were also applied to study the CSF but have provided little data with sufficient diagnostic specificity. In veterinary neurology, creatine kinase (CK) and lactate dehydrogenase (LDH) are sometimes measured. However, increased levels are found in a variety of different diseases and are considered to be nonspecific.

### **Other Metabolites**

Numerous metabolites were measured in the CSF, mostly in pathogenesis studies, to improve diagnostic work-up or to improve the prognostic value of the CSF examination. Changes in lactate and pyruvate levels may be indicative for a mitochondrial disease. The lactate:pyruvate ratio reflects the redox state in the brain. The measurement of these metabolites has only been performed in case reports, and values in large numbers of small animals and different diseases are lacking. The concentration of lactic acid in brain is dependent upon its rate of production and independent of blood lactate concentrations. Increased malondialdehyde (MDA) levels are an indicator for lipid peroxidation and was detected in the prefrontal cortex of dogs, but not in the CSF [31]. Gamma-aminobutyric Acid (GABA) is a major inhibitory neurotransmitter in the brain and spinal cord. Low levels of GABA were found in dogs with epilepsy [32-35]. A correlation was found between GABA concentrations in cerebrospinal fluid and seizure excitability. Treatment of dogs with seizures was also monitored by CSF examinations and the measurement of phenobarbital in the CSF [36]. The accumulation of excessive concentrations of glutamate in the extracellular space causes excitotoxic damage. Glutamate is considered to be a mediator of secondary tissue damage and elevated levels are found in several diseases [37,38]. Chronic and acute compressive spinal cord lesions in dogs due to intervertebral disc herniation are associated with elevation in lumbar CSF glutamate concentration [39]. Also biogenic amines were studied in the CSF and are of interest in studies in dogs with behavior abnormalities [40,41]. Changes in normal levels in serotonin, dopamine and norepinephrine are suspected to be important in aggressive dogs or in dogs with compulsive disorders. Low levels of neuropeptides such as orexin and hypocretin can be measured in dogs with sleeping disorders such as narcolepsy [42-44]. Numerous other metabolites were studied, mostly in pathogenesis studies on inflammatory/infectious diseases [45-49]: several cytokines (e.g., interferon gamma, interleukin 8, interleukin 10, transforming growth factor beta) were measured in canine distemper or steroid responsive meningitis-arteriitis in comparison to other CNS diseases [50-55]. An elevation of cytokine levels in the CSF is not specific for certain diseases. The CSF of inflammatory/infectious diseases can have chemotactic abilities for neutrophils and/or mononuclear cells [51]. Values for prostaglandins, lipids, neuropeptides, hormones and vitamins are known [1].

### **Intracranial Pressure (ICP)**

The intracranial cavity is closed by bony structures and its contents are fixed in total volume. The cavity is open through the foramen magnum into the spinal subarachnoid space with some degree of elasticity. Three components are important regarding the intracranial pressure: brain, CSF, and blood. Brain tissue may undergo displacement by herniation or by pressure atrophy as observed in hydrocephalus [3]. The volumes of intracranial blood and CSF vary reciprocally as described before, which help maintain intracranial pressure within normal limits. The regulation is performed by autoregulation of cerebrospinal blood flow and CSF absorption, but also by changes in body position [6].

Most dogs have a pressure between 5 and 12 mm Hg under general anesthesia, while slightly lower CSF pressures have been found in cats [4]. Causes for an elevated CSF pressure are space-occupying lesions (e.g., tumors), which cause compression of venous sinuses and therefore prevention of CSF absorption in the arachnoid villi. Elevated CSF pressure also occurs in cerebral edema, usually associated with brain injury, hydrocephalus and inflammatory lesions.

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## Neuroimaging ( 24-Jan-2002 )

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### Introduction

For most animals with suspected neurologic disease, conventional diagnostic radiography remains the preferred method of initial evaluation [1-9]. It is inexpensive, noninvasive, and readily available to most veterinary practitioners. However, radiographs significantly underestimate many abnormalities of the nervous system. The main limiting factors include superimposition of overlying structures, insufficient contrast resolution, and silhouetting by adjacent tissue or fluid of similar density. Advanced imaging techniques such as myelography, ultrasonography, scintigraphy, computed tomography, and magnetic resonance imaging are much more sensitive for detecting neurologic disease. For this reason, they are the preferred initial examination techniques in humans [10]. As advanced imaging techniques become increasingly available and less expensive, they are rapidly becoming standard diagnostic tools in veterinary neurology as well [2,7-9,11-20]. Neurodiagnostic techniques have been divided into the following categories:

### Conventional Diagnostic Radiography

- Basic Principles and Techniques
- Normal Findings
- Clinical Applications

### Myelography

- Basic Principles and Techniques
- Normal Findings
- Clinical Applications

### Scintigraphy

- Basic Principles and Techniques
- Normal Findings
- Clinical Applications

### Ultrasonography

- Basic Principles and Techniques
- Normal Findings
- Clinical Applications

### Computed Tomography

- Basic Principles and Techniques
- Normal Findings
- Clinical Applications

### Magnetic Resonance Imaging

- Basic Principles and Techniques
- Normal Findings
- Clinical Applications

### Conventional Diagnostic Radiography

Basic Principles and Techniques - Conventional diagnostic radiography is a technique in which images are exposed onto radiographic film using an x-ray tube [3,8,21-23]. Synonyms include plain, routine, or survey radiography. In conventional diagnostic radiography, x-rays are produced within the x-ray tube by the bombardment of a metal target with a stream of fast-moving electrons. Primary beam x-rays exit the tube, penetrate the patient and are differentially absorbed or transmitted by tissues. This differential absorption is affected primarily by x-ray beam energy and tissue properties such

as relative tissue density, thickness, and atomic number. Scatter radiation is also produced during tissue interactions and does not contribute to the image. The scatter radiation is absorbed by a grid, which is positioned between the patient and the film cassette. X-rays that pass through the patient and the grid directly expose the radiographic film and also cause a flash of light from the intensifying screen within the film cassette. The light flash from the intensifying screen contributes to 95% of film exposure and thus reduces the radiation exposure needed for a diagnostic radiograph. Those tissues or structures within the patient that absorb most of the x-rays are termed radiopaque. Those that allow most of the x-rays to be transmitted are termed radiolucent. Five basic densities (from most radiolucent to most radiopaque) are recognized on x-ray film: gas, fat, soft tissue, mineral, and metal [24]. Diagnostic sensitivity of radiographs is maximized by the use of good radiography equipment, film/screen combinations, technique charts, film processing techniques, and patient positioning [25]. Chemical restraint (heavy sedation or general anesthesia) is highly recommended to ensure accurate positioning [6,26,27]. Radiolucent positioning sponges, tape, or gauze also help to achieve symmetrical positioning and minimize personnel exposure. The use of a small focal spot and large object-film distance (air gap) may be used to help magnify smaller structures of interest [4,28]. The areas of clinical concern should be centered in the x-ray beam in order to minimize geometric distortion and maximize spatial resolution.

The standard radiographic views for the calvarium include lateral and dorsoventral projections [22,27,29]. To obtain true lateral positioning, padding is usually placed beneath the nose and neck. Dorsoventral views are obtained with the mandibles resting evenly on the cassette or table. The beam is centered on the midline between the eyes. Brachycephalic breeds may require more penetration than mesatocephalic or dolichocephalic breeds. Open-mouth and oblique projections are added as needed to improve visualization of the nasal cavity, frontal sinuses, tympanic bullae, calvarium, and foramen magnum. The open mouth ventrodorsal view is obtained with the patient placed in dorsal recumbency.

The mouth is held open with a speculum or gauze tied to the mandibular canine teeth. The tube is angled approximately 24 - 30 degrees caudally and the central beam is positioned in the midline at the level of the fourth maxillary premolar. The endotracheal tube is removed or pulled to the side with gauze. The frontal sinus view is obtained with the patient in dorsal recumbency and the neck slightly flexed so that the occipital condyles rest on the cassette or table. Once the patient is positioned, the beam is angled parallel to the nose. The calvarium and foramen magnum may be demonstrated in a 24 - 40 degree, closed mouth, rostrocaudal oblique projection. Lateral oblique and open-mouth, rostrocaudal projections are very helpful for visualizing the tympanic bullae. Lateral oblique views are obtained by positioning the patient in lateral recumbency, with the bulla of interest closest to the film.

The bulla is projected ventrally by placing a wedge sponge beneath the mandible. Opposite bulla views are recommended for comparison purposes. The open-mouth rostrocaudal projection is performed with the patient in dorsal recumbency and the mouth held open with a speculum or gauze (Fig. 1). The hard palate is tipped cranially, 3 - 12 degrees from vertical. Higher degrees of angulation are needed for brachicephalic breeds. The central beam is positioned in the midline at the back of the throat. The endotracheal tube is removed or tied to the mandible in the center of the mouth.



Figure 1. Positioning technique for rostrocaudal radiography of the tympanic bullae. (Courtesy Dr. Don Barber, Virginia Tech). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

The standard views for the spine are lateral and ventrodorsal projections [5,6,8,22,27]. For lateral views of the spine, rectangular foam or gauze pads are placed beneath the neck, a wedge sponge is placed beneath the nose and sternum, and a rectangular sponge is placed between the hindlegs. A weighted positioning sponge is used as needed to reduce curvature of the thoracolumbar spine. Forelimbs are pulled caudally for cervical spinal views and cranially for all thoracic spinal views. Hindlimbs are extended caudally for lateral views of the lumbar spine. For ventrodorsal views, sandbags or weighted positioning devices are placed on either side of the shoulders.

The head is elevated slightly using a thin rectangular foam pad or roll cotton. The hindlimbs may be flexed in a frogleg position, with wedge sponges supporting the stifle joints. Hindlimbs may also be extended, with the stifle joints elevated slightly to minimize lumbar lordosis. The central x-ray beam should be placed in the center of each spinal region of interest in order to minimize geometric distortion. Recently, a concave radiographic table was developed that allows radiography of the entire canine spine without the associated anatomic distortion [30]. Suspected vertebral instability may be assessed using flexed and extended lateral views [31]. The lateral oblique and open-mouth rostrocaudal views are helpful for improving visualization of the C2 odontoid process. The lateral oblique view is obtained by placing a wedge sponge beneath the caudal mandible and ventral neck regions. The odontoid process may be seen between the offset wings

of the atlas. The open-mouth rostrocaudal view is obtained using positioning similar to that described for the tympanic bullae. The odontoid process is positioned in the space between the bulla.

The endotracheal tube may need to be removed. Horizontal beam radiography can be used to obtain orthogonal views in animals with suspected spinal fractures or luxations. The patient is taped securely in lateral recumbency on a body board or stretcher, then placed on a thick foam pad that has been positioned on the x-ray table. Lateral views are obtained using standard techniques, with an increase of approximately 10 percent kVp to compensate for the stretcher and foam pad.

Ventrodorsal views of the region of interest are obtained by rotating the x-ray tube 90 degrees and centering the x-ray beam on the midline of the body. Image-intensified fluoroscopy may be used in conjunction with routine radiography to diagnose suspected atlanto-occipital or inter-vertebral instability [3,23]. It may also be used to guide placement of spinal contrast agents and to guide collection of tissue samples for cytology and culture/sensitivity.

### Normal Findings

*Brain* - The brain is not normally visible in plain radiographs, due to superimposition of overlying bone. The calvarium (cranial vault), which houses the brain, consists of 14 bones joined by sutures [32,33]. The calvarium is smoothly margined, with swirling convolutions on the dorsal and lateral surfaces. The cribriform plate is visible as a rostrally convex, curvilinear, bone opacity between the calvarium and the caudal nasal cavity. Open fontanelles may be visible in the dorsal calvarium in normal immature animals. Small breed dogs and cats have a more domed shape to the dorsal calvarium, and frontal sinuses may be poorly developed. The walls of the calvarium also appear thinner than those seen in large breed dogs.

*Spine* - The spinal cord and nerve roots are not normally visible in plain radiographs. The spinous process of C2 should be adjacent to or overlap the lamina of C1 (Fig. 2). The cervical articular processes are superimposed over the intervertebral foramina and vertebral canal in the lateral view. The C6 transverse process is large and projects ventral to the vertebral body (Fig. 3).



Figure 2. Lateral radiograph of the normal canine atlanto-axial junction. Notice the relationship between the C1 and C2 laminae. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 3. Lateral radiograph of the normal canine cervical spine. Notice the large C6 transverse processes. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Slight enlargements of the C5 - T2 and L2 - 5 spinal canal occur where the brachial and pelvic plexuses arise. There are normally narrowed intervertebral disk spaces at C7 - T1, T10 - 11, and T11 - 12. A mild loss of definition of the ventral margin of L4 may be due to the muscular attachments of the diaphragm [34]. The ventral portion of the L7 - S1 intervertebral disk space is often wider than the dorsal portion. The lumbosacral angle varies widely among individuals and is easily changed with flexion or extension of the spine. The dorsal margins of the sacrum and L7 vertebra should remain aligned, with no step defect. The hemal arches of the caudal vertebrae are visible as triangular or linear opacities ventral to the vertebral bodies in the lateral view. Use of a long scale of contrast, presence of a relatively high percentage of scatter radiation, and patient obesity may create an apparent decrease in vertebral opacity [35]. An artifactual increase in vertebral opacity may be caused by underexposure or use of a short scale of contrast (kVp too low).

### Clinical Applications

*Brain* - Because the brain is not visible in plain radiographs, diseases of the brain must be inferred from secondary changes in the skull. Calvarial enlargement, increased doming, or thinning of the bony wall are radiographic signs of congenital or acquired hydrocephalus [36] (Fig. 4). There may also be decreased visualization of the normal convolutions. The severity of distortion depends on the rate of fluid accumulation, severity of ventricular enlargement, and the stage of ossification at the onset of disease. Enlargement of the foramen magnum is a characteristic of occipital dysplasia [37-39] (Fig. 5).



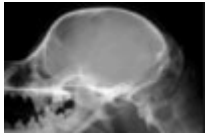


Figure 4. Lateral skull radiograph of a dog with hydrocephalus. (Courtesy Dr. Don Barber, Virginia Tech). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 5. Rostrocaudal skull radiograph of a dog with occipital dysplasia. There is dorsal elongation of the foramen magnum. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Some authors consider the malformation to be an incidental finding, especially in the Pekingese. Other authors theorize this malformation may cause an increased risk for intermittent tentorial herniation. Signs may include occipito-cervical pain, personality changes, scratching of one ear, protrusion of the tongue, dysphagia, ataxia, or convulsions. Neoplasms of the calvarium may cause invasion or compression of adjacent brain tissue. Lesions may be either osteolytic or osteoblastic. Most osteosarcomas of the cranial vault are osteoblastic, with regular well-defined borders and evenly distributed granular calcific densities [40]. Multilobular tumors of bone appear as lobulated, mixed soft tissue and bone opacity masses, which may or may not be locally invasive [41]. Synonyms include osteochondroma, osteochondrosarcoma, or chondroma rodens. In some cats, intracranial meningioma may be visible as a focal calcification or thickening of the calvarium [42] (Fig. 6).

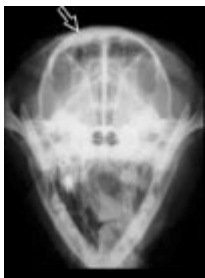


Figure 6. Rostrocaudal skull radiograph of a cat with intracranial meningioma. There is focal sclerosis of the right dorsal calvarium. (Courtesy Dr. Don Barber, Virginia Tech). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Middle ear disease may cause neurologic dysfunction if it causes inflammation of the vestibulocochlear nerve. Radiographic characteristics of middle ear disease include an increase in opacity of the affected bulla and associated thickening of the ventral bulla wall [43] (Fig. 7).



Figure 7. Rostrocaudal skull radiograph of a dog with left otitis media. There is increased thickness of the ventral bulla wall compared to that of the normal right bulla. (Courtesy Dr. Don Barber, Virginia Tech). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

In severe cases, the affected bulla may be expanded. With neoplastic disease of the middle ear, there may also be lysis of the petrous temporal bone and invasion of the cranial vault. In one study, 25 percent of dogs with surgically confirmed middle ear disease had negative radiographs [44]. Skull fractures may be associated with brain compression due to displaced fragments, or hematomas. Fractures are visible as radiolucent lines within the calvarium, which may or may not be associated with normal suture lines [45]. A step defect is visible when there is malalignment of the fracture fragments. Intracranial gas may be seen if there is a communication with the skin surface, nasal cavity or paranasal sinuses.

*Spine* - Radiographic signs of type I disk herniation include a focal mineral opacity in the vertebral canal or intervertebral foramen, narrowing or wedging of the intervertebral disk space, narrowing of the articular process joint space, or a decreased size of the intervertebral foramen [46,47] (Fig. 8a and Fig. 8b). Radiographic signs of type II disk herniation include narrowing of the disk space, sclerosis of the vertebral endplates, and spondylosis deformans (Fig. 9). Early

spondylosis may appear as faint bone spurs on the margins of the endplates [48].

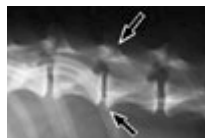


Figure 8a.



Figure 8b.

Figure 8a and 8b. Lateral and ventrodorsal spine radiographs of a dog with type I disc herniation at L1 - 2. There is narrowing of the intervertebral disk and articular process joint spaces. An amorphous mineral opacity is superimposed over the intervertebral foramen. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

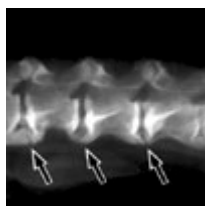


Figure 9. Lateral spine radiograph of a dog with type II disc herniation at L1 - 2, L2 - 3, L3 - 4, and L4 - 5. Notice the varying stages of spondylosis deformans. (Courtesy Dr. Don Barber, Virginia Tech). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Later on, the bone spurs may form a solid bridge across the intervertebral disk space. When the spondylosis forms ventrally and laterally, it does not cause nerve compression. When the spondylosis forms dorsally or dorsolaterally, it may cause stenosis of the vertebral canal or intervertebral foramina. Degenerative articular process joint disease appears as enlarged or irregular articular processes. Radiographic signs of atlanto-axial malformation/malarticulation include blunting or absence of the odontoid process, craniodorsal displacement of C2 relative to C1, and widening of the C1 - 2 interlaminar space [49] (Fig. 10). Block vertebrae are evident as absence of visualization of the articular process joint or intervertebral disk spaces [50].



Figure 10. Lateral spine radiograph of a dog with atlanto-axial subluxation. Notice the craniodorsal displacement and blunting of the dens, with widening of the C1 - 2 interlaminar space. (Courtesy Dr. Don Barber, Virginia Tech). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Depending on the portion of the vertebra that fails to form, a hemivertebra may be wedge-shaped with the base oriented dorsally, ventrally, or medially (Fig. 11). Neurologic dysfunction may occur when there is concurrent spinal stenosis, progressive spinal angulation with aging, or instability.



Figure 11. Lateral spine radiograph of a dog with hemivertebrae and dorsal angulation of the spine. (Courtesy Dr. Don Barber, Virginia Tech). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Ribs may be absent or hypoplastic at T13. This should be noted to avoid miscounts of vertebral levels at surgery. Vertebral osteochondromas or multiple cartilaginous exostoses appear as smoothly-marginated, mixed soft tissue and bone opacity masses. They may cause neurologic dysfunction due to spinal canal encroachment. Spina bifida is visible as an absence of spinous processes, or as a triangular or linear lucency in the vertebral lamina. This problem may be associated with other vertebral and neural anomalies, especially in Bulldogs and Manx cats [51]. Transitional lumbosacral vertebrae may appear as a caudal L7 vertebra with sacral characteristics (sacralization) or as sacral vertebrae with lumbar characteristics (lumbarization). Transitional lumbosacral vertebrae, in combination with degenerative disk disease, are predisposing factors for cauda equina syndrome in German Shepherd dogs [52]. One theory is that abnormal sacroiliac articulations may cause premature disk degeneration [53].

Hypervitaminosis A in the cat may be seen radiographically as irregular bone proliferation involving the ventral aspects of the caudal cervical and cranial thoracic vertebrae [54,55]. Feline mucopolysaccharidosis may cause partial fusion of cervical or lumbar vertebrae, irregularly shortened or misshapen vertebrae, widened intervertebral disk spaces, or an apparently widened spine [56]. Hyperparathyroidism is often characterized by a generalized decrease in bone density, with compression fractures of the vertebral bodies [57]. Vertebral neoplasms may be osteolytic, osteoblastic or both [58]. When there is extensive focal osteolysis, a compression fracture may be evident (Fig. 12a and Fig. 12b).



Figure 12a.



Figure 12b.

Figure 12a and 12b. Lateral spine and ventrodorsal thorax radiographs of a dog with metastatic mammary carcinoma. There is a compression fracture of the T6 vertebral body and a soft tissue mass in the caudal portion of the left cranial lung lobe. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

A paraspinal soft tissue mass may be visible adjacent to the affected vertebra. Focal enlargement of the spinal canal or intervertebral foramen can be found with slow-growing neoplasms of the nervous tissues. Another differential diagnosis for focal vertebral osteolysis/osteoproliferation is vertebral osteomyelitis [59,60]. Causes for vertebral osteomyelitis include migrating plant foreign bodies, aspergillosis, or bacterial infections. In spondylitis, the bony changes are most commonly centered within the vertebral body, and may involve several adjacent vertebrae. In diskospondylitis, bone changes are most often seen in adjacent endplates (Fig. 13). In physitis, the caudal vertebral physis appears widened and irregular. The caudal vertebral endplate may become sequestered and surrounded by an involucrum.



Figure 13. Lateral spine radiograph of a dog with lumbosacral diskospondylitis. There is widening of the intervertebral disk space with loss of definition of the caudal L7 and cranial sacral endplate margins. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Radiographic signs of vertebral trauma include changes in shape, opacity, margination, angulation or alignment [61]. Vertebral bodies may appear shortened or exhibit a triangular or trapezoidal shape. Fracture fragments may be visible as irregular bone opacities adjacent to the fracture site. Abrupt changes in spinal angulation may be associated with articular process luxation, compression fractures, or severe muscle spasms. Malalignment is visible as an abrupt change in the vertebral canal margin (step defect). Orthogonal views are very important, because malalignment may be apparent in only one plane (Fig. 14a and Fig. 14b).

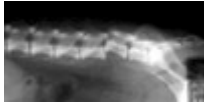


Figure 14a.



Figure 14b.

Figure 14a and 14b. Lateral and ventrodorsal spine radiographs of a dog with traumatic vertebral subluxation. The lateral view demonstrates severe dorsal displacement and caudal angulation of L6 relative to L5. This displacement is not apparent in the ventrodorsal radiograph. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

It is often helpful to hold the radiograph at an angle to the viewbox and look along the vertebral column to detect more subtle malalignments [6]. Dynamic vertebral subluxation may be demonstrated by comparing views obtained during flexion versus those obtained during extension [31].

## Myelography

**Basic Principles and Techniques** - Myelography is a radiographic examination that is performed after injection of an iodine-based contrast agent into the spinal subarachnoid space [22,62,63]. Non-ionic, isotonic contrast agents are preferred, due to their lower incidence of adverse reactions [64]. Commonly used myelographic contrast agents include iohexol and iopamidol. The contrast agent is injected into the cisterna magna or the lower lumbar subarachnoid space at a dose of 0.3 - 0.45 ml/kg. A 22 - 20 gauge spinal needle with stylet is used to minimize any damage caused by inadvertently piercing spinal cord tissue. For cisterna magna injection, the head is held in flexion and the needle is slowly introduced into the atlanto-occipital space. For lumbar injection, the hindlimbs are positioned in flexion and the needle is introduced into the L4 - 5 or L5 - 6 interlaminar space. The tip of the needle is most often positioned in the ventral portion of the lumbar subarachnoid space in order to minimize the risk of intramedullary injection. Because the needle penetrates the terminal portion of the spinal cord, care should be taken to minimize angular movement of the needle once it is in place. The bevel should be oriented cranially and the stylet removed to assess flow of cerebrospinal fluid (CSF). Correct needle placement may be confirmed using a test injection of a small dose of contrast and image-intensified fluoroscopy (Fig. 15). A pre-injection radiograph may also be obtained to assess needle position. Contrast injection is performed through a pre-filled, flexible extension tube in order to minimize needle movement. Lateral radiographs are obtained following contrast injection, while the needle remains in place. The needle is then removed for ventrodorsal views. Oblique and dynamic views are obtained as needed to clarify a suspected compressive lesion.



Figure 15. Photograph of image-intensified fluoroscopy machine. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Common myelographic artifacts include air bubbles, gravity filling defects, central canalogram, subdural injection, and epidural leakage. Air bubbles may cause oval or oblong filling defects in the subarachnoid space. Gravity may cause a regional decrease in subarachnoid filling. This is especially a problem in the cranial thoracic and thoracolumbar spine. It may be necessary to elevate the cranial and caudal portions of the spine to achieve filling in these regions. The central

spinal canal may be opacified (canalogram) due to iatrogenic injection of contrast agent into the central canal or due to a communication with the lumbar subarachnoid space. Contrast medium injected into the subdural space may cause an apparently widened dorsal column, with the ventral margin of the pooled contrast medium exhibiting a wavy or undulating shape [65]. The epidural space may also be inadvertently opacified when there is leakage of contrast outside the subarachnoid space (Fig. 16a and Fig. 16b). This is especially a problem when there have been multiple needle punctures. Epidural contrast leakage impairs visualization of the myelographic columns and may create a streaming effect at the intervertebral foramina.



Figure 16a.

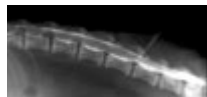


Figure 16b.

Figure 16a and 16b. Lateral lumbar myelogram images of a normal dog. A) Epidural leakage in the caudal lumbar and sacral regions. B) normal filling of the subarachnoid space. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

#### Normal Findings -

The spinal cord ends caudal to L6 in cats and small breed dogs [32]. The cord ends cranial to L6 in large breed dogs. The spinal subarachnoid space begins at the foramen magnum, and ends at the filum terminale. It is continuous with the intracranial subarachnoid space. The normal myelogram is characterized by discrete, thin columns of contrast medium that are nearly parallel. Exceptions to this rule may be seen in caudal cervical and caudal lumbar regions. In these locations, the myelographic columns may diverge slightly at the levels of the cervical and lumbar intumescences. Columns converge to a tapering point in the region of the conus medullaris. Small-breed dogs and cats have relatively large cords and relatively thin contrast columns [66]. The dorsal, ventral, and lateral columns should be of similar size at a given vertebral location. Exceptions to this rule may be seen in the cervical and lumbosacral regions. The ventral subarachnoid space is normally narrower than the dorsal subarachnoid space at C1 - 2. The ventral subarachnoid space is normally wider than the dorsal subarachnoid space in the lumbosacral region. The spinal cord may appear to be deviated dorsally in the caudal cervical and caudal lumbar regions, due to a relative increase in size of the ventral epidural space. The position of the dural end sac may be highly variable, depending on breed and the position of the hind legs [67,68]. Tortuous, curvilinear subarachnoid filling defects in the cranial cervical region are caused by the basivertebral artery and its branches. Caudally-oriented, linear filling defects in the lumbar subarachnoid space are caused by intradural nerve roots. Normal myelographic columns do not rule out spinal cord disease. Normal Findings may be associated with spinal cord atrophy, fibrocartilaginous emboli, myelitis, or meningitis [69]. Lumbosacral stenosis may also be present with a normal myelogram [70].

#### Clinical Applications - Myelography is indicated when:

1. There is absence of a spinal lesion on routine radiographs,
2. The lesion seen on routine radiographs does not correlate with the clinical signs,
3. Multiple lesions are seen on routine radiographs,
4. More precise localization of a lesion is needed for surgical planning,
5. More information on extent of involvement is needed for establishing a prognosis, or
6. The diagnosis of a neurologic disorder is established by absence of myelographic evidence of spinal cord compression (e.g., degenerative myelopathy) [62,69,71].

Some people consider CSF evidence of infectious disease to be a contraindication for myelography. Myelographic patterns of compression are classified as extradural, intramedullary, or intradural/extramedullary. Extradural compression is characterized by thinning and convergence of contrast columns (Fig. 17). Differential diagnoses for extradural compression include intervertebral disk herniation, ligamentous hypertrophy, epidural hematoma/hemorrhage, epidural or vertebral neoplasm, spinal stenosis, or vertebral subluxation/luxation.



Figure 17. Lateral thoracolumbar myelogram of a dog with type I disk herniation. There is dorsal displacement and narrowing of the ventral contrast column at L1 - 2. There is also narrowing of the opposing dorsal contrast column at this site. These changes are consistent with ventral extradural compression. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Intervertebral disk protrusion or herniation is one of the most common causes of extradural spinal cord compression, especially in chondrodystrophic dogs [72,73]. The myelographic contrast columns are deviated away from the site of disk herniation. Myelography is more sensitive than routine radiography for identifying the site(s) of disk protrusion [47,74]. When the disk protrusion is lateral to the midline, the ventral contrast column may appear forked or split [75]. Severe, chronic disk herniations may only exhibit mild deviation or narrowing of myelographic contrast columns. One possible reason for this is that chronic compression causes spinal cord atrophy, which in turn causes a relative increase in the size of the adjacent epidural space. It is the author's opinion that even mild narrowing of the myelographic contrast columns should be considered clinically significant when there is a localized decrease in spinal cord diameter. Normal cervical spinal diameters have been described for dogs [66]. In dogs with cervical vertebral malformation-malarticulation (wobbler) syndrome or cervical spondylomyelopathy, myelographic evidence of spinal cord compression may worsen with spinal extension and improve with spinal flexion or traction (Fig. 18a and Fig. 18b). Convergence of the contrast columns in both orthogonal views (hourglass appearance) may indicate concurrent spinal stenosis, hypertrophy of the ligamentum flavum or joint capsule proliferation.



Figure 18a.



Figure 18b.

Figure 18a and 18b. Lateral cervical myelogram of a dog with dynamic spinal stenosis due to cervical malformation/malarticulation.

A) The flexed view demonstrates mild ventral extradural compression at C6 - 7.

B) The extended view demonstrates ventral and dorsal extradural compression at C4 - 5 and C5 - 6, as well as dorsal extradural compression at C5 - 6. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Extradural neoplasms are more commonly centered at the mid-body of the vertebra. There may also be bone lysis on the side of the tumor or a paraspinal mass. Congenital spinal stenosis may cause segmental extradural compression in the canine thoracic or lumbosacral spine [50]. The dye columns may converge gradually or abruptly, depending on whether the stenosis is due to a uniformly small vertebral canal or to bulbous articular process joints. Because of the tapering shape of the caudal dural sac, myelography may underestimate lumbosacral canal stenosis in some dogs [7]. Spinal stenosis may occur as a separate entity or concurrently with vertebral anomalies such as hemivertebrae, or block vertebrae. Diskospondylitis may be associated with extradural compression in some dogs. In one recent study, the severity of myelographic compression did not correlate with severity of neurologic dysfunction [76].

Intramedullary compression is characterized by narrowing and divergence of contrast columns. Differential diagnoses include spinal cord edema, contusion, neoplasia, syringomyelia, hydromyelia, or granuloma. Acute type I disk herniation may cause a regional loss of myelographic filling due to spinal cord edema (swelling). Myelographic evidence of cord swelling was correlated with neurological outcome in a study of 46 dogs with intervertebral disk disease and absence of deep pain perception (DPP) [77].

Using a swelling L2 ratio of 5.0 as a cutoff for indication of neurological recovery yielded a sensitivity of 74% and a specificity of 61%. Overall neurological recovery rate was 43%. Intramedullary tumors may cause divergence and thinning of myelographic contrast columns in all views. Syringomyelia and hydromyelia may be distinguishable if there is a communication between the subarachnoid space and the central canal. Focal accumulations of contrast material will be

visible within the spinal cord parenchyma. Other differentials for central spinal cord opacification include hematomyelia or myelomalacia. Intradural/extramedullary compression is characterized by focal widening of the subarachnoid space, with or without an intraluminal filling defect. Intradural/extramedullary compression may be caused by subarachnoid cysts, intradural disk herniations, granulomas or neoplasms [78,79].

### **Ultrasonography**

**Basic Principles and Techniques** - Ultrasonography is an imaging technique that uses high frequency sound waves to visualize internal structures [21,80]. The sound waves are propagated from specially constructed ceramic materials called piezoelectric crystals. Real-time, B-mode imaging refers to the use of pulsed ultrasonography to obtain moving images of structures in gray scale. Images are constructed from returning echoes and continuously updated on the computer monitor by digital computer reconstruction. The brightness of the imaged structure is proportional to the strength of the returning echo. White structures are termed hyperechoic, gray structures are termed hypoechoic, and black structures are termed anechoic. The sound waves are both generated and received using a transducer or probe. Transducers are available in a variety of shapes and frequencies. The higher frequencies yield higher spatial resolution, but may not penetrate deeply enough in larger animals. Color flow Doppler ultrasonography and Doppler spectral analysis are used in conjunction with B-mode ultrasonography to evaluate blood flow. Color Doppler ultrasonography is performed first to determine the location of blood vessels. Blood flow is visible as areas of red, blue, yellow, or white on the ultrasound monitor. Electronic cursors may be placed within the lumen of vessels of interest to quantify blood flow velocity used Doppler spectral analysis. Velocity values are highest and the accuracy of the calculation is greatest when the angle of the ultrasound beam is parallel to the direction of blood flow.

Commonly encountered ultrasonographic artifacts include:

1. Refraction,
2. Reverberation,
3. Beam intensity, and
4. Beam thickness [80].

Refraction artifacts occur when there is a mismatch between ultrasound beam propagation speed and angle of inclination. These artifacts may cause surfaces in the far field to be erroneously placed within the center of the image. Reverberation artifacts are time-related and create repetitive images of structures. Beam intensity artifacts are created by either total reflection or total transmission of beam intensity. These cause either a shadow deep to the reflection (acoustic shadowing) or an increased intensity of echoes deep to the transmission (far enhancement). Beam thickness artifacts are created by the inclusion of both the wall and the lumen in the same image. This creates the false appearance of an intraluminal object.

Beam thickness artifacts are caused by the false assumption by the receiver that the beam is infinitely thin.

The brain can be imaged through craniotomy defects, open fontanelles or some of the larger neural foramina [80-82].

Some animals have sufficiently thin bone in the temporal region to allow transcranial imaging without a craniotomy defect. For most small animals, transducer frequencies between 7 and 12 MHz usually provide diagnostic quality images.

Imaging through the temporal bone may require the use of lower frequency probes, with some associated decrease in spatial resolution. Midline structures can be imaged using linear array, curvilinear, or sector transducers. Sector or curvilinear transducers are best for imaging peripheral structures. To image the brain through an open bregmatic (dorsal midline) fontanelle, the probe is placed over the fontanelle in an oblique transverse orientation. Images can be obtained in a rostocaudal direction using a "windshield wiper" motion. The probe is then rotated 90 degrees to obtain parasagittal images. To image the brain intraoperatively, the probe head and ultrasonic gel are placed in gas-sterilized plastic wrap. Sterile elastic bandaging material is used to wrap the probe stem and cord. Sterile physiologic saline is used to fill the craniotomy defect and provide an acoustic window for viewing brain tissues.

The spinal cord can be imaged through laminectomy defects, intervertebral foramina, noncalcified intervertebral disks, or defects caused by spina bifida [80,81]. Articular processes may need to be removed to evaluate dorsal root ganglia or nerve roots within the lateral recesses or intervertebral foramina. The small size of the spinal cord requires the use of a high frequency transducer (7.5- 12.0 MHz). For intraoperative ultrasonography of the spine, the probe and acoustic gel are placed in a sterile glove or plastic wrap, similar to the method described for intraoperative ultrasonography of the brain. Acoustic coupling is also performed by filling the surgical defect with sterile physiologic saline solution. Color flow Doppler ultrasonography and Doppler spectral analysis have been used to assess locations and flow velocities of spinal cord and nerve root blood vessels. The central spinal arterial system may be evaluated through a dorsolateral laminectomy defect [83]. The probe is oriented sagittally and angled 30 - 45 degrees from a plane perpendicular to the spinal cord. The dorsal root ganglion arteries may be evaluated through dorsolateral laminectomy and facetectomy defects [84]. The probe is oriented parasagittally, and angled caudolaterally.

### Normal Findings -

*Brain* - Normally visible brain structures include the falx cerebri, splenial sulci, cingulate gyrus, callosal sulci, lateral ventricles, third ventricle, caudate nuclei, thalamus, hippocampus, cerebellum, and osseous tentorium [81]. The gyri and sulci in neonatal brains are less well developed than those of mature brains. The hippocampi are less clearly seen in neonatal brains versus adult brains. In mid-transverse images of the brain, the paired splenial sulci and the longitudinal fissure appear as a hyperechoic (white) umbrella-like structure in the dorsal portion of the brain. The handle of the umbrella is made up of structures within the callosal sulcus. The corpus callosum appears as a hypoechoic horizontally oriented structure. In rostral transverse images, the superficial portions of the caudate nuclei appear as paired, oval, hyperechoic structures ventromedial to the lateral ventricles. The lateral ventricles are gull-wing shaped anechoic (black) structures. These may be difficult to see when there is insufficient CSF present. In one study, the mean height of the normal canine lateral ventricles, measured in transverse images at the level of the interthalamic adhesion, was 1.5 mm [85]. In the caudally oriented transverse images, the choroid plexus may be visible as a hyperechoic area in the floor of each lateral ventricle. Asymmetry between the lateral ventricles is common. The pyriform lobes are hypoechoic structures located ventrally on the floor of the cranium. In neonatal animals, the tentorium cerebelli, cerebellum, and medulla may be visible in the most caudal images. The tentorium cerebelli forms an inverted, hypercechoic, V-shaped structure. Deep to the tentorium, a stack of horizontal hyperechoic lines represents the vermis of the cerebellum. The cerebellar lobes appear as paired hypoechoic structures on either side of the vermis.

*Spine* - The spinal meninges are hyperechoic, the subarachnoid space is anechoic, and the spinal cord is homogeneously hypoechoic [83]. In some normal dogs, focal hyperechoic areas or linear echoes may also be seen within the spinal cord parenchyma. These may be caused by small intraparenchymal vessels. There is no differentiation between white and gray matter. Single or double linear echoes within the center of the spinal cord are associated with the central canal. The epidural space ventral to the spinal cord contains lobular echoes, presumably related to fat and connective tissue. The bony vertebral margin appears as a very bright, smooth echo with deep acoustic shadowing.

### Clinical Applications -

*Brain* - The most common application for brain ultrasonography is to determine the size of lateral ventricles in small breed dogs with suspected hydrocephalus [80,81]. Lateral ventricular enlargement is considered to be present when the mean height exceeds 0.35 cm [85] (Fig. 19). However, there is a poor correlation between ventricular size and severity of clinical signs. The second most common application is to evaluate the brain in animals with suspected intracranial neoplasia. Intraoperative ultrasonography may be used to guide surgical biopsy or excision of intracranial masses (Fig. 20).



Figure 19. Transverse ultrasonographic image of a dog with hydrocephalus. There is severe enlargement of both lateral ventricles. (Courtesy Dr. Martha Moon Larson, Virginia Tech). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

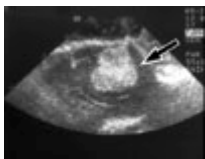


Figure 20. Sagittal, intraoperative ultrasonographic image of a dog with cerebral meningioma. The mass is hyperechoic relative to normal brain parenchyma. The zone of decreased echogenicity surrounding the mass is caused by edema. (Courtesy Dr. Martha Moon Larson, Virginia Tech). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

The size of a biopsied mass may be monitored after radiation or chemotherapy. The site of a surgically excised mass can be monitored over time to assess tumor regrowth. Most neoplasms appear hyperechoic. A technique for ultrasound-guided biopsy has been developed for use in dogs [86]. In this technique, the ultrasound probe is used to mark the biopsy site, then a needle guide is attached to the probe. The needle guide is adjusted to allow the needle to intersect the marked biopsy location. An incision is made in the dura to allow introduction of the biopsy needle into the brain mass. Ultrasonography may also be used to guide drainage of intracranial abscesses [81].

*Spine* - Common applications for ultrasonography of the spine include suspected retention of disk fragments, myelomalacia, intraparenchymal neoplasia, recurrent dural or spinal cyst [81]. Intraparenchymal hemorrhage appears as focal hyperechoic regions within the spinal cord. Retained intervertebral disk fragments appear as irregular hyperechoic foci, with or without acoustic shadowing, within the epidural space. The adjacent spinal cord may appear compressed. Spinal or arachnoid cysts appear as discrete anechoic lesions. Most spinal neoplasms appear hyperechoic. There may be



associated swelling of the spinal cord, with disruption or loss of the central canal linear echoes. Serial examinations may be helpful for differentiating neoplasia from intraparenchymal hemorrhage.

### Scintigraphy

**Basic Principles and Techniques** - Scintigraphy is a noninvasive imaging technique that is based on the selective accumulation of radioactive chemicals (radionuclides) within tissues [87,88]. Synonyms include nuclear imaging, planar scintigraphy, or nuclear scintigraphy. To perform the procedure, a small volume of the radionuclide is injected into the patient. The radionuclide can be used alone or attached to a chemical that will be selectively accumulated by the tissue of interest. The radionuclide emits gamma radiation as it decays to an inert form. A gamma camera records the gamma radiation emitted and converts it to an electrical signal (Fig. 21). A computer converts the electrical signal to digital information that is in turn used to create the image.



Figure 21. Photograph of gamma camera used for scintigraphy. (Courtesy Dr. Don Barber, Virginia Tech). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Tissues with a high concentration of radionuclides appear dark (hotspots). Areas with a low concentration of radionuclides appear white (coldspots). New software programs also allow color enhancement of the images. Hotspots can appear bright red or bright yellow if desired. Following the imaging procedure, the patient is kept in an isolated holding area until the radiation emissions are reduced to background levels (usually 1 - 3 days). The most common radionuclide used in veterinary medicine is technetium 99m (99mTc). It is preferred because the radioactive decay is very fast (half life about 6 hours), and the energy of the gamma rays emitted is relatively low. The main limitation of planar scintigraphy is the relatively low sensitivity for early intracranial or spinal cord disease that is obscured by superimposition of overlying structures. Newer, tomographic, scintigraphy techniques show promise for increasing the sensitivity of scintigraphy procedures. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) offer the advantage of functional imaging on a slice by slice basis [89]. Early alterations in cerebral/spinal blood flow and metabolism may be more quickly diagnosed in small animals if these techniques become less cost prohibitive in the future. Brain scintigraphy is most commonly performed using 99mTc-glucuheptonate, with dosages ranging from 5 - 35 mCi [9,87,88,90]. Images are acquired 1 - 4 hours after administration of radiopharmaceutical. The delay allows renal excretion of radiopharmaceutical from the blood pool, which in turn increased the lesion:background ratio of uptake. This improves the sensitivity of the procedure. General anesthesia is needed to insure precise positioning and control patient motion. Standard views include the right lateral, left lateral, dorsal, and caudal. Dorsal oblique views are obtained as needed to clarify a suspected lesion.

Spinal scintigraphy is most commonly performed using diphosphonate compounds such as 99mTc methylene diphosphonate (99mTc-MDP) [87,88,91]. When 99mTc-MDP is injected intravenously, it is first distributed in the blood pool then accumulates within the bone wherever there is active metabolism. Focal increases in uptake indicate locations where there is either increased blood flow or increased bone turnover. In small animals, doses typically range from 5 - 20 mCi. Three-phase bone imaging is a technique that is often used for distinguishing between soft tissue and bone lesions. Vascular phase images are initially obtained immediately after the injection. Soft tissue phase images are then obtained 10 - 20 minutes after injection. Images of bone accumulation (bone phase) are obtained 2 - 4 hours after injection.

### Normal Findings -

**Brain** - Normally there is a lack of radiopharmaceutical uptake in the brain parenchyma (Fig. 22). Radiopharmaceuticals are excluded from brain parenchyma by an intact blood brain barrier. Accumulation of radiopharmaceutical media within the surrounding skin, mucosal tissue, and muscle provide an outline for brain boundaries.

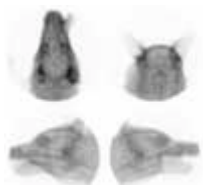


Figure 22. Brain scintigraphy image of a normal dog. There is no evidence of increased uptake within the cranial vault. (Courtesy Dr. Greg Daniel, University of Tennessee). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

*Spine* - The spinal cord is not visible in scintigraphic images, but diseases of the vertebrae and paraspinal tissues can be assessed. Normal vertebrae should exhibit uniformly low radiopharmaceutical uptake in bone phase images. Paraspinal soft tissues should exhibit low uptake in soft tissue window phases. In growing animals, focal increased uptake may be seen in metaphyseal regions (e.g., vertebral endplates). In older animals, focal increased uptake may be associated with vertebral degenerative changes (e.g., spondylosis deformans, degenerative articular process joint disease). These are of variable clinical significance.

#### Clinical Applications -

*Brain* - Scintigraphy of the brain is indicated when there is suspected intracranial disease, and when CT or MRI is either unavailable or cost-prohibitive. A positive brain scan is interpreted when there are regions of focal accumulation (hotspots) within the brain parenchyma (Fig. 23).

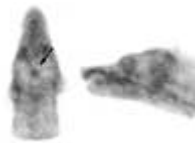


Figure 23. Brain scintigraphy image of a dog with cerebral ependymoma. There is a focal region of increased uptake within the cranial vault. (Courtesy Dr. Greg Daniel, University of Tennessee). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Focal accumulation of radiopharmaceutical media within the extracellular space is caused by disruption of the blood brain barrier. The lesions should be visible in multiple views to rule out superimposition from overlying structures. Differentials for a positive brain scan include neoplasia, necrosis, active hemorrhage, abscess, granuloma, or focal inflammation. In a retrospective study of 116 dogs and cats with proven intracranial disease, scintigraphy had a 75% sensitivity and a 90% specificity for focal brain disease [92]. Correlation of scintigraphic and radiographic findings may be helpful for confirming suspected intracranial masses. Scintigraphy is less sensitive for detecting degenerative or diffuse brain disease [88].

*Spine* - The most common applications for scintigraphy of the skull or spine are suspected osteomyelitis or neoplastic bone disease [88,91,93,94]. These diseases are visible in scintigraphic images much earlier than they can be seen with radiographs. When active soft-tissue disease is present, there is increased activity on vascular and soft tissue phases, but relatively normal activity on bone phase images. When active osteolytic or osteoproliferative disease is present, vascular and soft tissue phases may demonstrate some increased activity, but bone activity will be much more focal and intense (Fig. 24a and Fig. 24b). Differential diagnoses for focal regions of intense uptake include degenerative joint disease, trauma, infection or neoplasia. Definitive diagnosis of scintigraphic bone lesions usually requires further investigation with radiographs, CT, MRI, or biopsy.



Figure 24a.

Figure 24a and 24b. Bone phase forelimb and thorax images of a dog with metastatic neoplasia. There are multiple focal regions of increased uptake in the humerus, scapula, spine and ribs (Courtesy Dr. Don Barber, Virginia Tech). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

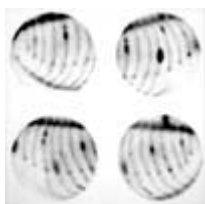


Figure 24b.

#### **Computed Tomography**

Basic Principles and Techniques - Computed tomography (CT) is a digital imaging technique that uses x-ray energy and computer processing to make cross-sectional (transverse) images of structures [21,95,96]. The x-ray tube is housed within



a ring-shaped structure called the gantry (Fig. 25).



Figure 25. Photograph of a CT scanner, demonstrating the patient table and gantry. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

A motorized table advances the patient through the gantry for each slice. Slices are made when the x-ray tube rotates in a circle around the patient. The energy of transmitted x-rays is recorded opposite the patient by detectors. Detectors convert the x-ray energy to an electrical signal. Each slice is divided into a matrix of cubes (voxels). A computer converts the electrical signal associated with each cube of tissue into numerical (digital) data. These data are referred to as CT numbers. They are units of density relative to water and are expressed in Hounsfield units (HU). Mean CT numbers are calculated for each cube of tissue and displayed as gray-scale picture elements (pixels) on the viewing monitor. White is assigned to pixels with higher CT numbers (e.g., bone). Varying shades of gray are assigned to pixels with intermediate CT numbers (e.g., soft tissues, fat and fluid). Black is assigned to pixels with lower CT numbers (e.g., lung, air-filled organs). The higher the number of pixels per unit volume of tissue, the higher the spatial resolution. The main advantages of CT over radiography are the ability to detect more subtle tissue density differences than radiography, elimination of superimposition, the ability to adjust image data as needed to improve visualization of structures. Operators can adjust the contrast (window width) and brightness (window level) of images as needed to better see tissues of interest. Bony structures are usually viewed at window widths greater than +500. Soft tissue structures are usually viewed at window widths less than +500.

CT scanners are classified in generations, with the numbers based primarily on technologic advancements in x-ray tube movement and detector design. Third generation scanners are configured such that the x-ray tube and arc of detectors rotate together around the patient for each slice. Fourth generation scanners have an x-ray tube that rotates around a stationary ring of detectors. Spiral (helical) CT scanners are the newest technology. With spiral scanning, the table moves continuously while the x-ray tube is rotating around the patient. This allows acquisition of all the volume data at one time, so that slice thickness can be altered retrospectively as needed. In spiral scanning, the table speed can be adjusted (pitch). The slower the table speed, the more samples are obtained per unit of tissue and the higher the image resolution. Extremely fast examination times are also possible (e.g., 30 seconds for a brain scan), but yield slightly lower image resolution.

A motorized patient table supports the patient in the center of the ring-shaped gantry opening. The maximum weight limit for most tables is 300 - 400 pounds. The table is incrementally advanced by the CT computer. This controls the slice thickness and intervals. The gantry houses the x-ray tube and detectors. The gantry can be tilted as needed to adjust angulation of the slices through the anatomic region of interest. A collimator, positioned between the x-ray tube and the patient, adjusts the thickness of beam. The detectors are positioned opposite the x-ray tube, so that they can record the amount of x-ray energy passing through the patient. The operator console of the CT computer controls the technique settings (kVp, mAs), slice thickness/interval, size of the area to be scanned (field size), size of the area to be displayed (image size), and the number of scans per slice. The CT computer processor creates the image from the numerical data. It also may be used to reformat the data in a set of CT images in order to view structures in the sagittal, dorsal, or oblique planes. Advanced computer processing techniques also allow three-dimensional reconstructions and selective color displays. Images are most commonly stored on x-ray film, using either a multi-format or laser camera. Digital image data are temporarily stored on the computer hard drive, then archived on tape cartridges or optical discs.

The most common CT artifacts are streak and partial volume artifacts. Streak artifacts appear as white or black lines that go across the CT image. Most are caused by errors in computer interpretation. Common kinds of streak artifacts include patient motion, density change, beam-hardening, and field of view. Patient motion causes parallel, blurred, white streaks in images. The streaks are oriented parallel to the direction of motion. Density change artifacts appear as bright white, sharp lines that radiate outward from a high density object (e.g., EKG lead, gunshot, bone plates). Beam hardening artifacts appear as black, blurred streaks across soft tissues adjacent to dense bone. This is especially a problem in the caudal fossa of the cranial vault (Fig. 26). Beam hardening artifacts are caused when dense bone differentially absorbs the lower energy portion of x-ray beam (e.g., cerebellum/brainstem).

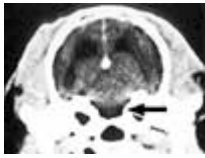


Figure 26. Transverse CT image of the caudal fossa in a normal dog. Beam hardening causes a black streak that obscures visualization of the brainstem. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Field-of-view artifacts appear as parallel, sharply margined, white lines across the whole image. They are usually caused by a body part or wire being positioned outside of the scanner's field of view. Partial volume artifacts appear as a false area of increased or decreased opacity in the image. They are caused by a voxel/pixel translation problem. The displayed gray-scale is determined from an average density of tissues within a given slice. If high density and low density tissues are adjacent to each other and included in the same slice, the computer averages their density and displays the gray-scale accordingly. Partial volume artifacts can be differentiated by looking at adjacent slices or re-scanning the area of concern using thinner slices. Other image quality factors include patient positioning, targeting, slice thickness, and scan speed [97]. It is important to make sure the anatomic region of interest is oriented perpendicular to the slice plane. Oblique positioning may cause a false positive diagnosis of anatomic asymmetry. Targeting is performed by choosing an image size that is limited to the region of interest (e.g., spine and paraspinal region). This allows the computer to enlarge the image and assign smaller pixels per unit area. Patients are placed under routine general anesthesia so that accurate positioning can be maximized and motion artifacts minimized.

For head imaging, we prefer sternal recumbency. The head is positioned within an extension cradle and adjusted as needed with foam sponges. The nose is slightly elevated such that the hard palate is parallel to the table surface. The endotracheal tube is taped to the extension cradle to avoid changes in head position as the table moves. Saphenous vein catheterization is preferred, but access to a cephalic vein catheter may be facilitated by positioning the forelimbs caudally. Lateral and ventrodorsal digital radiographs (pilot, scout image) of the region of interest is obtained with the CT scanner. Positioning is adjusted as needed and radiographs repeated. Transverse slices are posted on the final radiographs, with the cribriform plate as the first slice and the foramen magnum as the last slice. We use slice thicknesses of 2 mm for cats and small dogs, 4 mm for medium dogs, and 5 - 8 mm for large dogs. Image sizes range from 120 to 240 mm. Survey scans are first examined, then the scan is repeated immediately following a rapid intravenous injection of iodinated contrast medium (I) at a dose of 800 mg I/kg.

We also prefer sternal recumbency for the cervical spine. Positioning sponges are used to elevate the neck and sternum so that the caudal cervical vertebrae are in line with the cranial cervical vertebrae. For the thoracic, lumbar, and lumbosacral regions we prefer dorsal recumbency in order to minimize breathing motion artifacts. CT examinations with single slice scanners are usually limited to 3 - 4 disk spaces to avoid excessive scan times and tube heating. Scanning of larger spinal regions is more feasible with spiral CT scanners. Cost is more of a limiting factor in this situation, as scans are usually charged based on the total number of slices. Contrast enhancement can be performed either with intrathecal (post-myelogram) or intravenous administration of iodinated contrast medium. We prefer post-myelogram CT for suspected compressive lesions in the cervical, thoracic, and cranial lumbar spine. For suspected lumbosacral compression (L5 - S3), we prefer intravenous contrast-enhanced CT.

#### Normal Findings -

**Brain** - For a detailed identification of individual anatomic structures, the reader is referred to one of several published anatomic atlases [12,14,98-100]. In general, all normal paired structures should be symmetrical. Bony structures should be smoothly margined and well-defined. Cortical bone appears bright white and medullary bone exhibits varying shades of gray. The tentorium cerebelli may be calcified in some normal dogs [101]. Soft tissue structures are usually homogenous, with some variation in shades of gray caused by slight differences in tissue density (Fig. 27). To a limited extent, white matter can be distinguished from gray matter by a slightly lower density.



Figure 27. Transverse, post-contrast CT image of the middle fossa in a normal dog. Cerebral hemispheres are homogenous and symmetrical in shape. The white matter is slightly less opaque than the gray matter. The lateral ventricles appear as paired, linear lucencies. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

The ventricles of the brain appear slightly darker gray than brain parenchyma (hypodense), because the cerebrospinal fluid is approximately 2% less dense than brain tissue [98]. The fourth ventricle and its communication with the cerebellomedullary cistern help distinguish the cerebellum from the medulla. The position of the thalamus and interthalamic adhesion can be inferred from the relationship between the lateral and third ventricles. The intercrural cistern helps delineate the region of the pituitary gland. Bony landmarks such as the dorsum sellae, hypophyseal fossa, and

rostral clinoid process help in identifying the anatomic structures not distinguishable by their tissue density alone. After administration of intravenous contrast medium, there should be no focal enhancement within the normal brain parenchyma. The exception to this rule is the pituitary gland. This structure may enhance in normal animals, because there is no blood-brain barrier. Venous structures of the normal brain (intracranial venous sinuses, parenchymal veins, choroid plexus, falx cerebri) may enhance after administration of contrast material (Fig. 28).

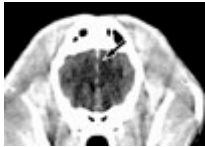


Figure 28. Transverse, post-contrast CT image of the rostral fossa in a normal dog. The falx cerebri exhibits contrast enhancement due to the presence of multiple small veins. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

*Spine* - Spinal cord white matter is normally indistinguishable from gray matter in CT images [12,102,103]. Structures contained within the thecal sac are also indistinguishable in plain CT images, but become visible when CT is performed post-myelography [11]. The outer margins of the thecal sac and nerve roots are visible in plain CT images, because they are surrounded by a layer of epidural fat (Fig. 29a, Fig. 29b and Fig. 29c). Epidural fat is less dense than soft tissue, so it will usually appear darker gray than adjacent nervous structures.



Figure 29a.



Figure 29b.

Figure 29a, 29b and 29c. Transverse and sagittal CT images of the lumbosacral spine in a normal dog. Radiolucent epidural fat in the vertebral canal and intervertebral foramen allow discrimination of nerve tissues. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 29c.

The normal intervertebral disk is of uniform soft tissue opacity, with no visible distinction between the nucleus pulposus and annulus fibrosus. The shape of the normal disk conforms to the shape of the adjacent vertebral endplates. The disk cannot be distinguished from the adjacent ventral and dorsal longitudinal ligaments. The dorsal margin of the combined disk and dorsal longitudinal ligament should be relatively flat. Venous structures of the normal spinal canal (vertebral venous plexus, intervertebral veins) may enhance after administration of intravenous contrast material [104]. Cortical bone is well-visualized in CT images. It is normally of a uniformly high opacity, with smooth margins. Cancellous bone has a lacy or honeycomb appearance. Focal lucencies within the marrow of the vertebral body can be associated with fatty degeneration in some older dogs. The articular process joint spaces are visible as thin, curvilinear lucencies between adjacent articular processes (Fig. 30).



Figure 30. Transverse CT image of the L6 - 7 disc space in a normal dog. Bone margins are smooth and symmetrical. Articular process joints are visible as paired curvilinear lucencies. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

### Clinical Applications -

**Brain** - The most common veterinary applications for head CT include suspected intracranial neoplasia, nonneoplastic brain disease, or vestibular disease. The general CT characteristics of brain disease include a visible mass; change in ventricular size, shape or position; deviation of the falx cerebri (falx shift), and focal change in brain opacity [9,13,15,16,18,20,97,105,106]. CT is more sensitive than MRI for acute hemorrhage, soft tissue calcification, and intracranial gas. CT is less sensitive than MRI for edema, infarcts, low grade masses, and caudal fossa masses. Administration of iodinated contrast medium intravenously helps improve visibility of many brain lesions. Contrast is administered using a rapid bolus injection of 800 mgI/kg. Focal accumulation of contrast medium in the brain parenchyma is a sensitive but not specific indicator of brain disease. Enhancement occurs in locations where there are venous sinuses, disruption of the blood brain barrier, damaged blood vessels, or malformed vessels (neovascularization). Because CT characteristics of brain lesions are not specific, cerebrospinal fluid analysis and brain biopsy are needed for a definitive diagnosis. New devices for minimally invasive, stereotactic, CT-guided biopsy of canine brain lesions have recently been developed [107-110]. New software features also allow CT dose planning for radiation therapy of intracranial masses [15,111] (Fig. 31a and Fig. 31b).

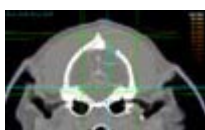


Figure 31a.

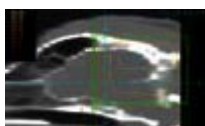


Figure 31b.

Figures 31a and 31b. Transverse and sagittal CT images of a dog following craniotomy for partial removal of a meningioma. The green rectangles represent the boundaries of radiation fields and other colored lines demonstrate the radiation dose distribution calculated by the treatment planning software. (Courtesy Dr. Don Thrall, North Carolina State). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Common characteristics of intracranial neoplasms in dogs and cats have been documented, but some overlap exists [15,16,18]. Meningiomas are usually peripherally located (extra-axial), broad-based at the edge of the brain or on the midline, markedly enhancing, and are large at the onset of clinical signs (Fig. 32). A "dural tail" may also be present. This is a region of linear enhancement that is associated with thickening of the dura mater adjacent to the mass. Meningiomas may also contain focal calcifications or be associated with bone remodelling (Fig. 33).



Figure 32. Post-contrast transverse CT image of a dog with cerebral meningioma. There is a broad-based, markedly-enhancing, sharply margined mass in the dorsolateral aspect of the left temporal lobe. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

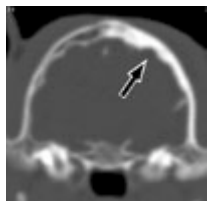


Figure 33. Bone window transverse CT image of the same dog illustrated in Figure 32. There is focal sclerosis and hyperostosis of the left dorsolateral calvarium. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Gliomas tend to be centrally located (intra-axial), peripherally enhancing (ring enhancement), and surrounded by a zone of edema (Fig. 34). Choroid plexus papillomas are often located either within or adjacent to a ventricle, appear hyperdense relative to surrounding brain tissue, exhibit marked enhancement, and are associated with hydrocephalus (Fig. 35).



Figure 34. Post-contrast transverse CT image of a dog with cerebral glioma. There is an irregular, ring-enhancing mass in the left frontal lobe. The falx cerebri is displaced to the right. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

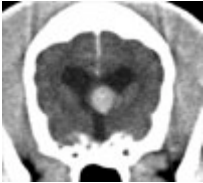


Figure 35. Post-contrast, transverse CT image of a dog with choroid plexus papilloma. There is a markedly enhancing, sharply-margined mass in the floor of the left lateral ventricle. Moderate generalized ventricular dilatation is also evident. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Pituitary macroadenomas and adenocarcinomas are most commonly located in the mid-ventral fossa of the cranial vault, displace the 3rd ventricle dorsally, enhance uniformly, and may exhibit a "mushroom cloud" shape (Fig. 36). New spiral CT techniques show promise for differentiating pituitary microadenomas based on changes in pituitary perfusion [112]. Metastatic neoplasia more commonly appears as multifocal regions of contrast enhancement, that may or may not be associated with ventricular displacement.



Figure 36. Post-contrast, transverse CT image of a dog with pituitary macroadenoma. There is a markedly-enhancing, sharply-margined mass that is centered over the pituitary fossa. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Hydrocephalus is evident as generalized or localized ventricular enlargement. Localized enlargement is more likely to be obstructive. Generalized enlargement is more likely to be nonobstructive. Asymmetry of the lateral ventricles may be indicative of obstructive hydrocephalus, but this finding has also been reported as a normal anatomic variant in some breeds. Edema may be visible as patchy areas of decreased opacity that are non-enhancing. Hemorrhage varies in opacity, depending on the duration [19]. Acute hemorrhage (24 - 72 hrs) appears as a region of increased opacity. Chronic (>72 hrs) hemorrhage usually exhibits a decreased opacity. Patchy regions of edema and increased meningeal enhancement may also be seen with inflammatory brain disease. Abscesses and chronic hematomas may mimic gliomas, in that they are often centrally located and ring-enhancing [113]. Inflammatory brain disease may mimic neoplasia in appearance [20]. There may be solitary or multifocal regions of contrast enhancement (Fig. 37).

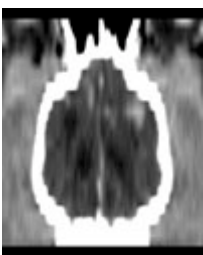


Figure 37. Post-contrast, dorsal planar CT image of a dog with fungal encephalitis. Multiple, ill-defined regions of contrast enhancement are present in both frontal lobes. The falx cerebri is displaced to the right. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Central vestibular disease may be underdiagnosed in CT images, due to beam hardening artifacts in the caudal fossa. However, CT is very sensitive for identifying middle ear disease in small animals [114]. A previous study found that the diagnostic sensitivity for detecting middle ear disease was similar for radiographs and CT [115]. However, this has not been the author's experience. It is possible that CT resolution has recently improved with advances in scanner technology. Otitis media is visible as an increased soft tissue opacity in the bulla lumen. With chronicity, there may also be thickening and sclerosis of the bulla walls, or expansion of the bulla (Fig. 38). Otitis media may be associated with nasopharyngeal polyps, especially in cats. Middle ear neoplasia is more commonly characterized by lysis of the bulla or extension into the cranial vault (Fig. 39a and Fig. 39b).

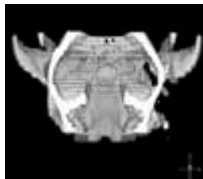




Figure 38. Transverse CT image of a dog with otitis media. There is thickening and sclerosis of the left tympanic bulla wall. Increased soft tissue opacity is also present in the ventral portion of the bulla and in the horizontal portion of the external ear canal. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 39a. and 39b.



Figures 39a and 39b. Transverse post-contrast and three-dimensional CT images of a cat with squamous cell carcinoma. An ill-defined, heterogeneously-enhancing soft tissue mass involves the right external ear canal and tympanic bulla. There is lysis of the floor of the cranial vault, with enhancement of the meninges adjacent to the bone defect. The three-dimensional image demonstrates the size of the bone defect. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

*Spine* - The most common applications for spine CT include suspected intervertebral disk disease, spinal stenosis, or spinal masses. CT is often less sensitive than MRI for discriminating soft tissues within the spinal canal [8,11]. However, CT is more sensitive than MRI for soft tissue calcifications, cortical bone spurs, and degenerative changes in the articular process joints. Type I intervertebral disk herniation is visible as either single or multiple bone opacity masses in the intervertebral canal, intervertebral foramina, or extraforaminal region (Fig. 40).

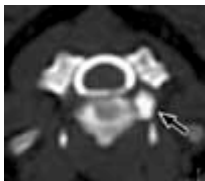


Figure 40. Transverse, post-myelogram CT image of a dog with cervical type I disk herniation. The myelographic contrast column appears normal. An irregular, sharply margined bone opacity is present in the left intervertebral foramen. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Type II disk herniation is characterized by circumferential bulging of the annulus, narrowing of the intervertebral disk spaces, endplate sclerosis, and endplate bone spurs (spondylosis deformans). Other signs of chronic degenerative disk disease may include endplate fragmentation, Schmorl's nodes, and vacuum phenomena. Schmorl's nodes are sharply margined endplate lucencies that are caused by intravertebral disk herniation. They may mimic diskospondylitis, but usually exhibit more peripheral sclerosis. Vacuum phenomena are air opacities that are seen within the intervertebral disk or vertebral endplates. They are formed when nitrogen gas is forced out of the disk capillaries under pressure. Vertebral fractures are visible as linear lucencies, bone fragments, and may be associated with subluxation. Intraspinal hemorrhage may be apparent as amorphous, soft tissue opacity material within the vertebral canal. There may be concurrent traumatic herniation of disk material and spinal cord compression. Vertebral neoplasia is suspected when there is a paraspinal mass, contrast-enhancing soft tissue in the vertebral canal, bone destruction or active proliferation, or pathologic fractures [58] (Fig. 41). Intramedullary neoplasms may sometimes be demonstrated with intravenous enhanced CT, however MRI is far more sensitive.

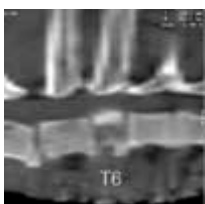


Figure 41. Sagittal, bone window CT image of a dog with thoracic spinal osteosarcoma. A large osteolytic lesion is present within the center of the T6 vertebral body. There is an associated compression fracture, with displacement of the dorsal fracture fragment into the vertebral canal. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Intradural/extramedullary neoplasms are best demonstrated with CT myelography. Focal widening of the subarachnoid space, spinal cord compression, subarachnoid filling defects are all characteristic of intradural/extramedullary neoplasms. Expansion of the vertebral canal or intervertebral foramina may be seen, especially with slower growing neoplasms. Diskospondylitis is characterized by ill-defined, osteolytic lesions within adjacent endplates [76] (Fig. 42).

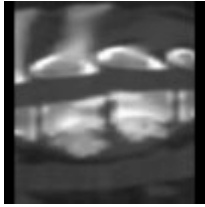


Figure 42. Sagittal, bone window CT image of a dog with thoracolumbar diskospondylitis. There is focal osteolysis of the T13 - L1 vertebral endplates with active bone proliferation on the ventral aspects of the vertebral bodies. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

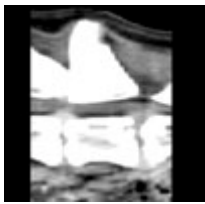


Figure 43. Sagittal, soft tissue window CT image of a dog with degenerative lumbosacral stenosis. There is bulging of the L6 - 7 and L7 - S1 disc margins, with loss of epidural fat ventrally and dorsally. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

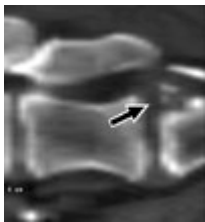
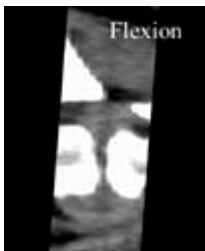


Figure 44. Parasagittal, bone window CT image of a dog with degenerative L7 - S1 disk disease and sacral endplate fragmentation. There is blunting of the craniodorsal sacral margin with a bone opacity fragment adjacent to the defect. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

The disk margin may bulge outward and exhibit contrast enhancement. There may be an associated loss of epidural fat due to canal encroachment by protruding disk material or infiltration by inflammatory tissue (eg. meningomyelitis). Spondylitis may sometimes mimic neoplasia in appearance. There are often mixed osteoproliferative/osteolytic lesions involving one or more vertebral bodies. There may be contrast-enhancing soft tissue within the vertebral canal. However, paraspinal masses are less commonly seen with spondylitis than with neoplasia in this author's experience. Congenital or idiopathic spinal stenosis is visible as thickened lamina and pedicles, bulbous articular processes, and an abnormal shape to the bony canal [116]. There is also a loss of epidural fat within the vertebral canal and/or intervertebral foramina. Soft tissues causing encroachment on the nerve roots or thecal sac often exhibit enhancement after administration of intravenous contrast medium [104]. Characteristics of degenerative stenosis include bulging of the disk margin, spondylosis, endplate sclerosis, hypertrophied ligamentum flavum, hypertrophied joint capsules, congestion of the venous structures, or subluxation (Fig. 43). Fragmentation of the vertebral endplate may occur with severe degenerative disc disease or preexisting sacral osteochondrosis [117] (Fig. 44). Dynamic subluxation is demonstrated by comparing mid-sagittal views obtained with the spine in flexion versus those obtained with the spine in extension (Fig. 45a and Fig. 45b).



Figures 45a. Sagittal, flexion and extension CT images of a dog with lumbosacral stenosis and dynamic subluxation. There is cranioventral displacement of the sacrum relative to L7 and increased narrowing of the L7 - S1 vertebral canal with extension of the spine. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figures 45b. Sagittal, flexion and extension CT images of a dog with lumbosacral stenosis and dynamic subluxation. There is cranioventral displacement of the sacrum relative to L7 and increased narrowing of the L7 - S1 vertebral canal with extension of the spine. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

## Magnetic Resonance Imaging

**Basic Principles and Techniques** - Magnetic resonance imaging (MRI) is an imaging technique that uses a strong magnetic field and pulses of radiofrequency energy to cause tissues to emit characteristic energy signals [21]. A motorized table centers the patient in a tube-shaped or open gantry in which there is a constant strong magnetic field. While inside the gantry, hydrogen atoms within the patient's tissues align themselves with the magnetic field. Tissues are intermittently exposed to brief pulses of radiofrequency energy to temporarily knock the hydrogen atoms out of alignment. A weak energy signal (resonance) is released from the tissues as the hydrogen atoms realign themselves with the magnetic field. A receiver coil is placed near the anatomic region of interest to record the signal coming from the tissues. The strength of the returning signal varies based on multiple factors: inherent tissue factors, concentration of hydrogen atoms, interactions of the atoms with each other, strength of the magnetic field, technique settings assigned by the computer operator, duration of each radio-pulse, frequency of radio pulses (repetition time or TR), and how long the signal is recorded by the receiver coil after the pulse occurs (echo time or TE). The MRI computer converts the signal intensity to varying shades of gray in the image. Tissues with higher signal intensity are assigned whiter colors. Those with lower signal intensities are assigned darker gray colors. Tissues having no signal appear black.

MRI system components include a magnet, receiver coil, computer station, and gradient coils. The magnet maintains a strong external magnetic field around the patient. The magnetic strength is measured in Tesla units (1 Tesla = 10,000 X earth's magnetic field). Three ranges of magnetic field strength are available for medical MRI scanners:

1. low field = < 0.5 Tesla,
2. mid field = 0.5 - 1.0 Tesla, and
3. high field = > 1.0 Tesla.

The two most common types of magnet construction are superconducting or permanent. Superconducting magnets are made using coils of electrical wires that are cooled with liquid helium or nitrogen. Permanent magnets consist of magnetic discs, usually made of iron. The receiver coil detects the electromagnetic signals being emitted by the tissues. Receiver coils are available in different sizes and shapes, so they can be as close to the area of interest as possible. This helps maximize the signal to noise ratio and improve image quality. The computer station controls the technical parameters and radiofrequency pulse sequences. The plane of scanning can be altered without moving the patient by the use of gradient coils. These gradient coils cause slight changes in the main magnetic field, that are used as localization tools by the MRI computer.

Numerous radiofrequency pulse sequences have been designed in order to improve visualization of specific tissues of interest. The possibilities are nearly endless. However, the most commonly used pulse sequence is the spin-echo technique. This involves the use of a 90 degree radiofrequency pulse followed by a 180 degree radiofrequency pulse. T1-weighted images are created when short TE and short TR intervals are used in a spin echo pulse sequence (eg. 20 - 35 ms, 300 - 500 ms respectively). Tissues that appear bright white in T1-weighted images include fat, gadolinium contrast medium, and proteinaceous fluid. Tissues that appear dark on T1-weighted images include all other fluids, edema, air, bone, and fast-flowing blood. Proton-density weighted images are created using short TE and long TR intervals e.g., 20 - 35 ms and 1500 - 2500 ms respectively). Fluid appears dark, fat appears white, and the gray matter appears brighter than the white matter. T2-weighted images are created using long TE and long TR intervals (e.g., 75 - 150 ms, 1500 - 2500 ms respectively). Tissues appearing bright white in T2-weighted images include fluid and edema. Tissues that appear dark on T2-weighted images include soft tissue, air, bone, and fast-flowing blood. Other pulse sequences used for small animal MRI may include fluid-attenuated inversion recovery (FLAIR), diffusion-weighted, magnetization transfer, and fat-saturation techniques.

Common MRI artifacts include motion, ferromagnetic, signal void, and signal drop-off. Motion appears as blurred streaks that run perpendicular to the direction of motion (Fig. 46). They are present in all images obtained during a given pulse sequence. Ferromagnetic artifacts are caused by such objects as gunshot fragments or pellets, vascular clamps, skin



staples, intravenous catheter needles, or orthopedic fixation devices. These artifacts appear as a large black void that surrounds the metallic object (Fig. 47). The void may obscure all adjacent structures or distort their shape.

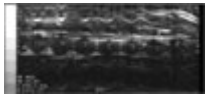


Figure 46. Sagittal, T2-weighted image of a dog with degenerative lumbar spinal stenosis. Motion artifacts appear as wavy, parallel, longitudinal streaks across the entire image. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

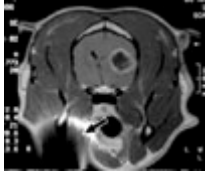
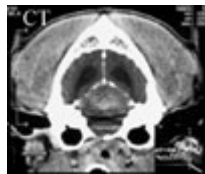


Figure 47. Transverse, T1-weighted, post-contrast image of a dog with cerebral glioma. A metallic artifact obscures visualization of the right retropharyngeal region. The artifact was caused by a metallic needle within the dog's cephalic catheter. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

High field strength magnets may also cause metallic objects to move or heat up during scanning. A signal void artifact is caused by fast-moving blood within a vessel. The protons that are knocked out of alignment by the radiofrequency pulse move out of the scan field before they can release their resonating signal. Signal drop-off artifact occurs at the edges of the receiver coil. As the signal-to-noise ratio drops, the image becomes increasingly dark and grainy in appearance.

The main advantages of MRI versus CT include:

1. No beam hardening artifacts,
2. Higher sensitivity for subtle changes in soft tissue chemical properties,
3. The ability to acquire images in any plane desired, and
4. Absence of ionizing radiation (Fig. 48a and Fig. 48b). For example, MRI is much more sensitive than CT for early infarcts and edema.



Figures 48a. and 48b.

Figures 48a and 48b. Transverse post-contrast CT versus post-contrast MRI in a dog with cerebellar glioma. The mass is partially obscured by beam-hardening artifacts in the CT image. With MRI, the extent of the mass is more clearly distinguishable. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



The main disadvantages of MRI vs. CT include:

1. Higher cost,
2. Shifting or heating up of metallic implants,
3. Severe distortion artifacts caused by metallic objects in the scan field,
4. More sensitive to motion artifacts and
5. Less sensitive for soft tissue calcification or bone proliferation.

High field magnets cannot be used for patients or personnel in early pregnancy or with cardiac pacemakers. The intravenous contrast agent most commonly used is gadolinium. This is a paramagnetic substance that causes adjacent hydrogen nuclei to relax more quickly. Tissues accumulating gadolinium have shorter T1 times and therefore appear bright in T1-weighted images. Causes of focal enhancement are similar to those previously described for CT. Future

developments of contrast material for MR imaging include non-gadolinium compounds, intrathecal contrast media, cerebral blood flow and volume evaluation, and, possibly, antibody-labeled contrast agents [118]. Recent advances in MR scanner technology also allow evaluation of intracranial vessels without the use of intravenous contrast material. The procedure is termed magnetic resonance angiography (MRA), because it resembles a conventional angiogram in appearance [119]. Image formation takes advantage of the fact that a signal void phenomenon occurs in regions with fast-moving blood. Pulse sequences are designed to selectively display regions where a signal void is present, without displaying the overlying structures. Three-dimensional reconstructions of blood vessels may also be created, so that the anatomic relationships can be more readily appreciated.

In the spine, some of the advantages of MRI versus CT include:

1. Earlier detection of Intervertebral disk degeneration,
2. Ability to differentiate the spinal cords and nerve roots from CSF ("myelogram effect"),
3. Higher sensitivity for intramedullary neoplasia, and
4. Ability to evaluate an entire region of the spine in a single examination (e.g., cervical, thoracic, lumbar).

One of the main disadvantages is the difficulty in getting good resolution in small-sized animals (less than 25 lbs). Often, image quality can be limited due to a low signal-to-noise ratio and partial volume averaging. Also, limited sensitivity for bony changes may make MRI less desirable for evaluating bone spurs, articular process joint disease, or calcified soft tissue masses.

#### Normal Findings -

*Brain* - For a detailed identification of anatomic structures, the reader is referred to one of several published anatomic atlases [12,120]. As with CT, all normal paired structures should be symmetrical. There should be no focal contrast enhancement (with the exception of the pituitary gland, veins, and sometimes the choroid plexus). T1-weighted images yield the best spatial resolution and morphologic detail for soft tissues overall [120]. However, there is poor to moderate contrast between the gray and white matter of the brain. Cerebrospinal fluid within the ventricles and subarachnoid spaces exhibits very low signal intensity and appears dark gray or black. Ventricles are normally well-visualized in dogs, but may be more difficult to appreciate in cats [121]. Ventricular asymmetry may be present as a normal anatomic variant, especially in beagles and labrador retrievers [122,123]. Fat in the bone marrow of the skull, subcutaneous tissue, and fascial planes has high signal intensity and appears bright white. Proton-density weighted images yield an image very similar to T1-weighted images, with improved contrast resolution between gray matter and white matter. White matter has slightly lower signal intensity than gray matter. T2-weighted images are of overall lower signal intensity compared to other pulse sequences and yield darker images. The spatial resolution is also decreased, with a more grainy appearance. This technique provides the best contrast resolution between gray and white matter of the brain. Also, cerebrospinal fluid within the ventricles and subarachnoid spaces appears bright white. In all pulse sequences, arteries and veins with fast-moving blood exhibit low signal intensity because of signal void artifacts. Cortical bone also appears dark black in all pulse sequences because the protons are so rigidly bound they cannot move out of alignment when pulsed. Air within the tympanic bullae, nasal cavities, frontal sinuses, and nasopharynx also appears black in all pulse sequences, due to the low concentration of hydrogen protons.

*Spine* - In general, the spatial resolution of CT for evaluation of the spine is higher than with MRI. However, the superior contrast resolution of soft tissues offers a significant advantage [11,124-126]. On T1-weighted images, the intervertebral disk is of uniformly medium signal intensity, slightly greater than that of the spinal cord, nerve roots, and bone marrow. Epidural fat has very high signal intensity and appears bright white (Fig. 49). The cerebrospinal fluid around the spinal cord has lower signal intensity and helps distinguish the margins of the nervous tissue structures from adjacent fat.

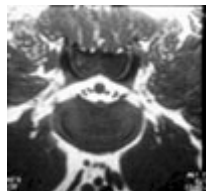


Figure 49. Transverse, T1-weighted image of the L6 - 7 vertebral canal in a normal dog. High signal intensity fat facilitates visualization of lower signal intensity nerve roots. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

In T2-weighted images, normal intervertebral disks consist of a high signal nucleus pulposus surrounded by a medium signal annulus fibrosus. The variation in signal intensity is related to varying concentrations of ground substance. Ground substance contains hyaluronic acid and glycosaminoglycans, which in turn attract and hold water. The nucleus pulposus normally possesses the highest concentration of ground substance, and therefore has the highest T2 signal intensity. The

cerebrospinal fluid also has high signal intensity. The subarachnoid space can be seen as a zone of increased signal intensity that surrounds the spinal cord and nerve roots (myelogram effect). The central canal is visible as a thin, linear region of increased signal intensity within the center of the spinal cord. Epidural fat exhibits intermediate signal intensity, higher than spinal cord or nerve roots. Vertebral marrow is of lower signal intensity than either fat or the spinal cord. In all pulse sequences, cortical bone has low signal intensity. Spinal ligaments and joint capsules are also of low signal intensity, making them mostly indistinguishable from cortical bone. Short segments of the dorsal and ventral longitudinal ligaments can be distinguished where they span the intervertebral disk space. The ligamentum flavum is partially visible at some interlaminar spaces.

#### Clinical Applications -

*Brain* - Common veterinary applications for head MRI are similar to those for head CT: suspected intracranial neoplasia, non-neoplastic brain lesions, or vestibular disease [16,19,20,114]. Also similar to CT, typical MRI characteristics of common brain neoplasms have been established and there are some exceptions to the rules. A definitive diagnosis still requires a biopsy. Meningiomas usually have an extra-axial location, are broad-based and appear sharply margined. They are isointense in pre-contrast T1 weighted images, hyperintense in T2-weighted images, and uniformly enhancing (Fig. 50). Choroid plexus adenomas are most commonly found in intraventricular or cerebellopontine locations.

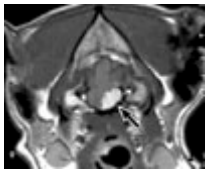


Figure 50. Transverse, post-contrast, T1-weighted image of a dog with brainstem meningioma. The mass is broad-based, markedly-enhancing, and sharply margined. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

They are solitary, and often associated with hydrocephalus. They appear isointense in pre-contrast T1 weighted images, hyperdense in T2-weighted images and are uniformly enhancing. Gliomas typically have an intra-axial location. Ependymomas and oligodendrogliomas are often periventricular. Medulloblastomas are often in the cerebellum. Gliomas tend to be hypointense in pre-contrast T1 weighted images, and hyperintense in T2 weighted images. They exhibit variable enhancement (Fig. 51a and Fig. 51b). Low grade gliomas may not enhance at all. High grade gliomas may have cavitory areas and marked peritumoral edema. Pituitary adenomas are in the suprasellar region and are usually fairly sharply margined. They appear isointense in pre-contrast T1 weighted images and are often uniformly enhancing.



Figure 51a.



Figure 51b.

Figures 51a and 51b. Dorsal planar, T1 post-contrast and T2 weighted images of a dog with cerebellar glioma. The mass is T1-hypointense, non-enhancing and T2-hyperintense. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Characteristics of nonobstructive and obstructive hydrocephalus are similar to those described for CT. With MRI, periventricular edema may be easier to see as an indicator of possible acute hydrocephalus or inflammation. Periventricular edema appears as a zone of increased T2 signal intensity that surrounds the ventricles. Obstructive hydrocephalus secondary to a Chiari I malformation may also be more readily identified with MRI. The most common form is the Chiari I malformation, which is characterized by caudal displacement of a portion of the cerebellum through the foramen magnum (Fig. 52). Syringohydromyelia of the cervical spine may also be present [127].

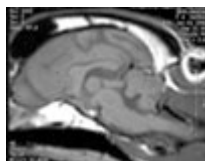


Figure 52. Sagittal, T1-weighted image of a dog with Chiari I malformation. The caudal margin of the cerebellum is flattened, with protrusion of the caudoventral margin through the foramen magnum. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Intraparenchymal hemorrhage varies in signal intensity, based on the stage of hemoglobin breakdown [19,128]. Within the first few hours, a hematoma will usually be T1-hypointense and T2-hyperintense. In the first few days, the T1 signal may vary from hypointense to hyperintense while the T2 intensity remains hypointense. As hemolysis occurs over the next few weeks, the T1 intensity ranges from hyperintense to hypointense, while the T2 signal becomes more consistently hyperintense. Non-hemorrhagic infarcts are usually visible with MRI earlier than with CT. Initially, the infarct may appear hyperintense in T2 and proton-weighted images (Fig. 53).



Figure 53. Dorsal planar, T2-weighted image of a dog with cerebral infarction. A T2-hyperintense, periventricular lesion is present in the right frontal lobe. There is no displacement of adjacent structures. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Parenchymal enhancement is uncommon within the first few days. After several weeks, the infarct decreases in size. There is often focal atrophy of the adjacent brain tissues, with dilation of nearby sulci and ventricles. In experimental canine studies, MRI was found to be more sensitive than CT for identification of early meningitis. [129] Post-gadolinium T1-weighted images demonstrated increased leptomeningeal enhancement earlier than enhancement was seen with CT. Early intraparenchymal edema from encephalitis may be seen as ill-defined regions of increased T2 signal intensity, primarily within the white matter. Encephalitis may also be associated with ventricular asymmetry. Ring-enhancing abscesses may mimic gliomas. Multifocal, contrast-enhancing granulomas may mimic metastatic neoplasia. Vascular disorders may also mimic a solitary brain neoplasm. Magnetic resonance angiography can be used to noninvasively depict aneurysms, malformations, occlusive disease, and fistulas [119] (Fig. 54a and Fig. 54b).

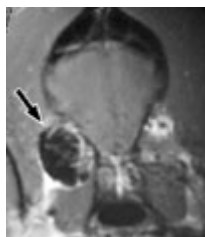


Figure 54a. Transverse, post-contrast T1-weighted and MRA images of a dog with suspected orbital arteriovenous fistula. A T1-hypointense, non-enhancing mass is present in the right orbit. MRA demonstrates high signal intensity within the right orbital veins. The mass exhibits a mixed signal intensity, consistent with fast or turbulent blood flow. (Reprinted with permission from: Tidwell AS, et al. Computed tomography and magnetic resonance imaging of cavernous sinus enlargement in a dog with exophthalmos. *Vet Radiol & Ultras* 1997; 38:363-370.) - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 54b. Transverse, post-contrast T1-weighted and MRA images of a dog with suspected orbital arteriovenous fistula. A T1-hypointense, non-enhancing mass is present in the right orbit. MRA demonstrates high signal intensity within the right orbital veins. The mass exhibits a mixed signal intensity, consistent with fast or turbulent blood flow. (Reprinted with permission from: Tidwell AS, et al. Computed tomography and magnetic resonance imaging of cavernous sinus enlargement in a dog with exophthalmos. *Vet Radiol & Ultras* 1997; 38:363-370.) - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

MRI is much more sensitive than CT for identifying central vestibular disease, primarily due to the absence of beam

hardening artifacts in the brainstem [114,130]. Peripheral vestibular disease is evident as an increased T1 and T2 signal intensity within the lumen of the affected tympanic bulla [130-132]. Post-gadolinium T1-weighted images may help differentiate free fluid from proliferative soft tissue. Sclerosis of the bulla wall cannot be identified when there is air in the lumen, due to a lack of signal from both air and cortical bone. Neoplastic middle ear disease may demonstrate T2-hyperintense tissue both inside and outside the tympanic bulla (Fig. 55).

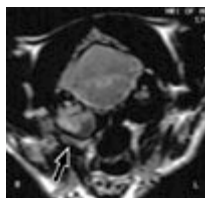


Figure 55. Transverse, T2-weighted image of a cat with middle ear squamous cell carcinoma. There is mixed signal intensity tissue within the right tympanic bulla, external ear canal and para-aural region. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

*Spine* - Common applications for spinal MRI in animals include suspected degenerative spinal disease, early diskitis, neoplasia, or syringohydromyelia [7,11]. Degenerative disk disease is characterized by a decreased T2 signal intensity within the nucleus pulposus [124-126] (Fig. 56). Degenerative lumbosacral stenosis is evident as a focal loss of epidural fat within the vertebral canal or intervertebral foramina. This finding is often associated with intervertebral disk protrusion, displacement of nerve tissue, and low signal tissue encroaching on ventral and dorsal vertebral canal.



Figure 56. Sagittal, T2-weighted image of a dog with degenerative lumbosacral disk disease. There is decreased signal intensity within the L7 - S1 disc. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Intervertebral disk protrusion is characterized by dorsal displacement of the disk margin, fragmentation, or loss of the normal ovoid shape of the disk. In one canine experimental study MRI had a sensitivity of 93%, specificity of 97%, and accuracy of 95% for diagnosing disk infection [93]. Early diskitis is evident as increased signal intensity or contrast enhancement of the intervertebral disk. With diskospondylitis, there is also increased T2 signal intensity or contrast enhancement that extends into the adjacent vertebral endplates or vertebral bodies. Vertebral endplate margins may appear irregular or fragmented. Epidural abscesses may exhibit ring enhancement in post-gadolinium T1-weighted images. In humans, MRI is considered to be the modality of choice for suspected spinal neoplasia [10]. It has been found to be more sensitive than scintigraphy for vertebral metastases [133]. Neoplasms most commonly appear hyperintense in T2-weighted images and exhibit contrast enhancement in post-gadolinium T1-weighted images. They are of variable T1-signal intensity. Arachnoid cysts are nonneoplastic masses that may cause spinal cord compression in humans and animals [10,78,134,135]. These lesions are similar to neoplasms in that they appear hyperintense in T2-weighted images, but they do not enhance with contrast. They are most commonly found in the intradural-extramedullary space. Syringohydromyelia is a focal accumulation of fluid within the spinal cord central canal or parenchyma [136]. It may be developmental or acquired. Developmental syringohydromyelia may remain subclinical until it is exacerbated by concurrent spinal cord compression due to other causes. In T2-weighted sagittal images, syringohydromyelia is readily apparent as a tubular region of high signal intensity within the center of the spinal cord.

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## **Canine Rehabilitation** (20-Feb-2003)

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### **Introduction**

The field of physical therapy/rehabilitation has much to offer veterinarians in terms of its application to sporting dogs as well as orthopedic and neurologic patients. In 1978, canine physical therapy techniques were described by Ann Downer, a physical therapist on faculty at Ohio State University [1]. More recent texts on canine physical therapy are becoming available [2,64]. The purpose of this chapter is to present an overview of rehabilitation methods. The procedures described here are applicable to dogs with various neurological disorders, as well as dogs with orthopedic disorders.

Some of the physical therapy methods that can be adapted to canine rehabilitation include:

1. Thermal Agents (ice, hot packs, therapeutic ultrasound, diathermy)
2. Phonophoresis and Iontophoresis for Transcutaneous Drug Delivery
3. Electrical Stimulation
4. Therapeutic Exercise
5. Aquatic Therapy
6. Goniometry
7. Orthotics (braces/splints)
8. Exercise Prescriptions
  - a. Joint Contracture
  - b. Thoraco-lumbar Intervertebral Disk Disease, Non-weight-bearing in Pelvic Limbs
  - c. Thoraco-lumbar Intervertebral Disk Disease, Weight-bearing in Pelvic Limbs
  - d. Lumbosacral Disease, Post-operative
  - e. Anterior Cruciate Ligament Rupture, Post-operative

### **1. Thermal Agents**

Superficial heating agents penetrate to a depth of approximately one centimeter. Deep heating agents can elevate tissue temperatures at depths of three centimeters or more. Deep heating agents include ultrasound and diathermy. As a general rule, cold therapy ("cryotherapy") is indicated during acute inflammation when the lesion exhibits signs of redness, swelling, pain and/or heat. Heat is indicated during the sub-acute and chronic inflammatory phases. Ice application is also indicated to resolve swelling after exercise. In some cases, such as the treatment of muscle spasm and spasticity, the therapist may need to use a trial and error method to determine if either heat or cold yields clinical improvement. In humans, ice is usually not applied for longer than 15 minutes at one time in order to avoid reflex vasodilation. This guideline seems prudent for animals, also.

The indications for alternating heat and cold ("contrast baths") include impaired venous circulation and indolent ulcers, and traumatic or inflammatory conditions during the subacute or chronic phases. The mechanism of action of contrast baths is production of alternating vasoconstriction and vasodilation of local blood vessels. This reaction is considered to stimulate blood flow to the treated area and thereby to help stimulate healing.

### **Therapeutic Ultrasound**

Two physical therapy modalities utilize ultrasound. These modalities are therapeutic ultrasound, which produces deep heating of tissues, and phonophoresis, which utilizes ultrasound waves to move drugs through intact skin (Fig. 1).

Therapeutic ultrasound delivers ultrasound waves through a transducer head comparable in size to the heads used in diagnostic ultrasound (Fig. 1). As with diagnostic ultrasound, the transducer must be in contact with the skin surface. With therapeutic ultrasound, however, the ultrasound waves increase tissue temperatures at depths up to 3 - 5 cm or more. Energy within an ultrasound beam decreases due to scatter and absorption as the waves travel through tissue. Scattering is the deflection of sound when the beam strikes a reflecting surface. In contrast, absorption is the transfer of energy from the sound beam to the tissues. Absorption is high in tissues with a high proportion of protein [3,4] and minimal in adipose tissue [3,5]. This means that ultrasound penetrates subcutaneous fat with little attenuation, whereas tissues with a high collagen content absorb more of the energy.



Figure 1. Portable ultrasound equipment (Courtesy of Chattanooga Medical Supply). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Therapeutic ultrasound has both thermal and non-thermal effects. The non-thermal effects have been studied primarily in wound healing. The thermal effect of therapeutic ultrasound is a major indication for its use. Increases in tissue temperatures of 1 to 4°C are associated with increases in collagen extensibility, blood flow, pain threshold, and enzyme activity. In humans, the rate of increase in tissue temperature is directly related to the frequency of the ultrasound waves (MHz) and the intensity (watts/ cm<sup>2</sup>). Experimentally, when tissue temperatures were compared at various depths (0.8 to 5.0 cm) using thermistors inserted into muscles, the rate of temperature increase per minute ranged from 0.04°C at 0.5 W/cm<sup>2</sup> to 0.38°C at 2.0 W/cm<sup>2</sup> for 1 MHz treatment and from 0.30°C at 0.5 W/cm<sup>2</sup> to 1.4°C at 2.0 W/cm<sup>2</sup> for 3 MHz treatment [6]. Clearly, the 3 MHz treatment heated the tissues faster than the 1 MHz treatment at all intensities.

**Techniques** - Several techniques have been outlined for the use of therapeutic ultrasound in horses [4,7-9]. To minimize reflection of the ultrasound beam at air-tissue interfaces, a coupling medium must be applied between the sound head and skin. Direct coupling, under water immersion, and coupling cushions have been described for dogs [10]. **Direct coupling** is preferred when the skin surface is flat and is larger than the applicator surface (Fig. 2). A commercially available, water-soluble gel is applied to the skin and the sound head. The gel may be pre-heated. Coupling agents NOT recommended are electroconductive gels, lanolin-based compounds and mineral oil. The **underwater immersion method** was popular before smaller transducer heads became available [4]. Immersion can be considered when the skin surface is so uneven that direct contact is difficult, such as occurs in the distal limbs of the dog. The part to be treated can be immersed in a container of tap water at room temperature, but both the water and skin must be clean. Water in a whirlpool is not recommended if it has been agitated. Because metal containers reflect some of the ultrasound beam, which could increase the intensity in areas near the metal, rubber or plastic containers are preferred as they cause less reflection. The transducer should be held underwater 0.5 - 3.0 cm from the skin. The intensity may be increased by 0.5 W/cm<sup>2</sup> to compensate for absorption of the ultrasound by water [3]. Immersion has not compared favorably with direct coupling in several studies in which tissue temperatures achieved by these two methods were compared [14,60]. One protocol for treating humans consists of applying ice to the treatment area prior to ultrasound therapy. Adding ice to the water for ultrasound delivered underwater has been recommended for horses [8]. However, if the aim is to increase tissue temperature, then it appears that ultrasound therapy in combination with ice would yield little benefit. A **coupling cushion** is a third alternative for delivering ultrasound [10], for example, placing a water-filled balloon between the transducer head and the skin, with coupling gel at the interfaces [11].

Commercially available gel pads are preferable. A recent in vitro study compared the transmissivity of commercial gel pads, water-filled latex gloves, gel-filled latex gloves, gel-filled condoms and water bath immersion through pig skin from which the hair had been clipped [61]. They recommended that if the direct method could not be used because of the contours of the treatment surface, then the therapist should use commercially available gel pads.



Figure 2. Direct coupling is preferred when the skin surface is relatively flat and is larger than the surface of the transducer. Ultrasound gel is applied to the skin and the transducer. (Courtesy of Dr. P. Shealy, Veterinary Specialists of the Southeast, Charleston, SC, USA). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

What about the hair coat? - The presence of the hair coat may be a major drawback to ultrasound treatment and phonophoresis in dogs. Because ultrasound energy is absorbed by tissues with a high protein content, and deflection of the ultrasound beam occurs at tissue interfaces, it would be expected that ultrasound penetration through the hair coat into underlying tissues would be poor. For horses, one investigator [7] has specifically recommended clipping the hair and using adequate coupling gel, or standing the horse in water to reduce the air interface, although immersion will not prevent the scattering due to the hair coat. We conducted a study in dogs to quantify temperatures in underlying tissues when ultrasound was delivered through intact hair coats, using commercial ultrasound gel at room temperature [12]. In that study, ultrasound delivered through either short or long hair coats produced only minimal temperature increases in underlying tissues, compared to the responses achieved when the hair had been clipped. Furthermore, there was considerable warming within the hair coat. Even hair coats as short as those of Greyhound dogs inhibited tissue heating. Future research is needed to determine if modifications such as warming the ultrasound gel might enhance ultrasound penetration through the intact hair coat.

Treatment Variables - Tissue heating depends on frequency, intensity, duration, treatment area and the characteristics of the tissue. Ultrasound beams are considered collimated such that frequencies in the megahertz (MHz) range expose a limited target area. **Frequency** determines depth of penetration. As the frequency of the ultrasound waves increases, penetration decreases. One MHz heats at depths around 2 - 5 cm [12,13]. Three MHz heat at depths around 0.5 - 2 cm [4,13,59]. Consequently, treatment of superficial lesions can be problematic if the unit delivers only 1 MHz. If there is underlying bone, then most of the ultrasound will hit the bone and the intensity cannot be turned up very high to heat the underlying soft tissue before the patient feels periosteal pain [13]. An area of study which is currently receiving attention is the use of low frequency (long wave) ultrasound (< 1 MHz frequencies). **Intensity** refers to the rate of energy delivery per unit area. The power meter in an ultrasound unit indicates both watts and watts/cm<sup>2</sup>. Intensities typically range from 0.25 to 3.0 W/cm<sup>2</sup>. The greatest intensity within the beam is termed "spatial peak intensity". The "beam non-uniformity ratio" compares the maximal intensity from the transducer to the average intensity, and should be low (2:1 to 6:1) to indicate that energy distribution is relatively uniform, with minimal risk of tissue damage from areas of concentrated ultrasound energy ("hot spots"). The higher the intensity, the larger and faster the temperature increases. Generally, intensities required to elevate tissue temperature to the range of 40 - 45°C vary from 1.0 - 2.0 W/cm<sup>2</sup> with continuous wave mode for 5 - 10 min. If there is less soft tissue and/or bone close to the surface, lower intensity and higher frequency are appropriate. In any case, the patient's tolerance is the final determinant [3].

Several therapists have observed that dogs sometimes whine or seem uncomfortable 5 - 10 min after commencing therapeutic ultrasound. Any distress that animals show should be assumed to be due to pain and the therapist should either reduce the intensity or terminate the session. Most therapists use intensities that produce no detectable sensation in human patients. However, some experts are advising that the intensity be increased until the person feels vigorous heating of the tissues and then be lowered [13]. This difference in opinion has probably come about because the heating effects in the underlying tissues are difficult to monitor. Therefore, although tissue damage can result from excessive ultrasound exposure, there is also the possibility of insufficient exposure. **Duty cycle** refers to the fraction of time that the sound is emitted during one pulse period. In **continuous mode**, the ultrasound intensity is constant, whereas a **pulsed wave** is interrupted in an on-off manner. Typical duty cycles range from 0.05 to 0.5. Pulsing may be used when the desired effect is based on a non-thermal mechanism or when heating is to be minimal, such as treating near bone [4]. The **duration** of treatment is short, typically 10 minutes or less. Duration of a session can be estimated as 5 min/25 in<sup>2</sup> treatment area [13]. Five to ten minutes are necessary for adequate tissue heating. For instance, in one study it took nearly 8 minutes for the temperature to reach therapeutic levels at a depth of 3 cm in the gastrocnemius muscle in humans [14]. In that study, a direct coupling technique was used, with continuous mode, at 1.5 W/cm<sup>2</sup> and the sound head was moved at 4 cm per sec. At an intensity of 1.5 W/cm<sup>2</sup> and a treatment area twice the size of the effective radiating area of the transducer, it has been recommended that treatment duration be approximately 3 - 4 minutes at 3 MHz or 10 minutes at 1 MHz [13]. Our findings with 1 MHz in dogs support these recommendations [12]. **Treatment area** should be 2 - 3 times the size of the effective radiating area of the transducer head [13]. Increasing the treatment area decreases the effective heating of the tissues. **Speed of the sound head** over the skin is usually recommended to be approximately 4 cm per sec [11] to achieve uniform distribution of energy. Moving the transducer too quickly diminishes heating and makes the therapist prone to cover too large an area. The transducer should NEVER be stationary. Because the ultrasound beam is non-uniform, some target areas could receive a large amount of energy with the risk of causing "hot spots" and cavitation. **Treatment schedules** may be daily initially, followed by less frequent sessions as the condition improves [3]. Bromiley has indicated that treatment can be daily for up to 10 days, but should not exceed two 10 day courses without a 3 week rest [4]. Grant has made similar recommendations for horses [7].

Precautions and Contraindications - Tissue burns can occur if the intensity is too high or the transducer is held stationary. These factors can put the patient at risk for cavitation, a phenomenon whereby bubbles of dissolved gas form and grow

during each rarefaction phase. Also, if the transducer is held in the air while emitting ultrasound, the face of the transducer will overheat. The end result could be damage to the ultrasound transducer or tissue damage if the transducer contacted the animal's skin. Some units have a built-in system to prevent the transducer from overheating. Some ultrasound energy is unavoidably emitted through the housing of the sound head to the therapist's hand, but the effects of this "parasitic" exposure are unknown.

It is important to avoid direct ultrasound exposure to the following: cardiac pacemakers, carotid sinus or cervical ganglia, eyes, gravid uterus, heart, injured areas immediately after exercise [7,9], malignancy, spinal cord if a laminectomy has been performed, testes and contaminated wounds. One should exert caution in considering ultrasound therapy in the following situations: tissue near a bone fracture or bony prominences, tissue that has been treated with cold packs or ice, decreased circulation, decreased pain/temperature sensation (animals should not be overly sedated, restrained or under local anesthesia) and epiphyseal areas in immature animals [4,11]. Also, there is evidence that intracapsular heating may accelerate destruction of articular cartilage in acute inflammatory joint disease [3]. Although metal implants are not necessarily a contraindication, the effects of ultrasound on cementing compounds such as methyl methacrylate are unknown [11].

Clinical Applications - In human rehabilitation, ultrasound therapy has been used for many years, but it is only quite recently that this modality is being evaluated with controlled clinical trials. In some regards, the jury is still out regarding the role of ultrasound therapy. Clinical trials and outcome assessments remain to be done in veterinary medicine. In horses, ultrasound therapy has been suggested for the treatment of tendinitis, desmitis, sprains, joint lesions, lacerations, scar tissue reduction, edema, exostosis and myositis [7,8]. In human athletes, some experts consider that the most beneficial results from ultrasound are in treating tendonitis [13]. In chronic tendinitis, recommended therapy includes heating with ultrasound, followed by cross-frictional massage. Another indication is treatment of limited range of motion associated with joint contracture, for which patients receive ultrasound therapy before passive range of motion or joint mobilization techniques. A third indication is pain relief prior to activity, such as for an athlete with tendinitis which is mild enough that the person can continue training; ultrasound treatment is administered prior to activity to assist in the warm-up and provide some pain relief. **Tendinitis and bursitis** are treated with ultrasound to increase blood flow, increase temperature to reduce pain and drive anti-inflammatory drugs across the skin by means of phonophoresis. In humans, lateral epicondylitis, sub-acromial bursitis, and bicipital tendinitis are typical indications for ultrasound therapy. Animal studies suggest that the stage of healing at which ultrasound therapy is administered is important, as ultrasound during early tendon repair could be detrimental [11].

The principle of "heat and stretch" can be applied in cases of **joint contracture and scar tissue** in an effort to increase range of motion. Tissues are first heated by ultrasound and then passively or actively stretched by the therapist. The effects of heat on ligament extensibility were studied in healthy humans [15] who underwent knee joint displacement tests before and after continuous ultrasound therapy (1 MHz, 1.5 W/cm<sup>2</sup> for 8 minutes). The investigators reported only minimal increases in the extensibility of some knee ligaments after this form of treatment. Because **scar tissue** is denser than surrounding tissues, it can be heated selectively. However, more research is needed to determine optimal intensities and durations needed to affect scar tissue. **Pain threshold** usually increases after ultrasound therapy, although the physiological mechanisms underlying pain reduction remain speculative. Heating could increase the activation threshold of free nerve endings which mediate pain sensation, produce counter-irritation, or activate large diameter nerve fibers [11]. Non-thermal mechanisms also may play a role in pain relief. The mechanism of action for reduction of **skeletal muscle spasm** may rely on thermal effects that alter the skeletal muscle contractile process, reduce muscle spindle activity, or break the pain-spasm-pain cycle [11]. Additional research is needed to determine the mechanism of action of ultrasound therapy on the different stages of **wound healing** and the optimal treatment parameters. The results in wound healing appear to depend on the intensity and duration of treatment and the time after injury. Low intensities appear to enhance healing whereas high intensities may have pro-inflammatory effects. Similarly, ultrasound therapy initiated within the first week after injury may compromise tissue repair whereas the same treatment initiated after 2 weeks may be beneficial. Dyson reported that ultrasound enhanced growth of tissue in experimental wounds in rabbit ears [16]. Because the temperature increases were small, the investigators suggested that the mechanism involved acoustic streaming, a biophysical response to ultrasound energy.



Figure 3. Diathermy is another method to obtain deep heating of tissues. In this figure, a single drum unit is applied over the hamstring muscles in a German Shepherd dog with fibrotic myopathy. The layer of towelling is used as spacing when the drum is positioned over the limb. However, research remains to be done to document the heating effects of diathermy in small and large animals. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Other Conditions - Claims have been made that ultrasound treatment causes **calcium resorption**. A recent study confirmed

that ultrasound therapy was associated with an increased rate of calcium resorption in humans with calcific tendonitis of the shoulder [17]. The ultrasound-induced excitation of calcium bound to proteins may promote the fragmentation and resorption of calcified masses within soft tissue [4]. Ultrasound also may have a role in **reduction of swelling**, but this remains to be validated.

## 2. Phonophoresis

Phonophoresis refers to the use of ultrasound to enhance the delivery of topically applied drugs to the underlying tissues. In humans, the most common use of phonophoresis is for treatment of localized musculoskeletal inflammatory conditions. Hydrocortisone [18], dexamethasone [19,20], salicylates, indomethacin [21,22] or lidocaine [11] are incorporated into a vehicle such as glycerol, cream, oil or water for skin application. Ultrasound is then applied over the area in an effort to drive these substances into the tissues. The major limiting factor has been low skin permeability [23]. Current research focuses on maximizing absorption of drugs and determining which drugs can be applied with this method [20]. Low-frequency phonophoresis can enhance the transdermal delivery of proteins such as insulin and interferon [23,24]. Research in animals should be directed toward documenting drug penetration through the skin, and the effect of the hair coat.

*The section on Therapeutic Ultrasound and Phonophoresis was adapted with permission from Steiss JE. Physical therapy in veterinary medicine: Therapeutic ultrasound and phonophoresis. Comp Cont Edu Pract Vet 2000; 22:690-693 [55].*

## Iontophoresis

Introduction - Methods of transdermal drug delivery include iontophoresis and phonophoresis. Iontophoresis ("ion transfer") is a form of electrotherapy. Certain drugs which ionize in solution can be driven into the skin and underlying tissues by direct current applied through surface electrodes. Since an electrode will repel similarly charged ions, positively charged ions can be introduced into the tissues by the positive electrode (anode); ions with a negative charge can be introduced by the cathode.

Effective skin penetration of a variety of drugs has been documented in humans and laboratory animals. Therefore, it is reasonable to expect that this technique could be applied in veterinary medicine. The potential uses for iontophoresis could be of particular interest to veterinarians dealing with musculoskeletal conditions in performance animals and to anesthesiologists. The information presented here is taken from basic research articles and literature on the treatment of humans, primarily athletes.

Equipment and Techniques - The procedure and instrumentation are relatively straightforward [25]. Direct current (DC) is required to ensure the unidirectional flow of ions during the procedure. A typical battery-operated unit incorporates a control for adjusting the current output, an ammeter to measure the current, a voltage control knob and meter, and a timer. The size of units is small enough to make them easily portable (Fig. 4). In the United States, several companies market iontophoresis units. The prices vary from approximately \$500 - \$1000. New iontophoresis units ("IontoPatch"), which are currently marketed for human use, have adhesive electrodes with a built-in battery for continuous drug delivery.

The factors which determine the amount of drug introduced into the tissues include the polarity, intensity and duration of the current, the electrode size, skin resistance, ionization potential, and nature of the solvents. Typical **current intensity** is in the range of 3 - 5 milliamps (mA) with **treatment duration** of 10 - 20 min. For humans, the sensation of the stimulation can be used to gauge intensity. When initiating treatment, the current intensity usually is increased slowly until the person reports feeling a tingling sensation [25]. A guideline which could be followed in treating animals is to set current amplitude to deliver a current density between 0.1 and 0.5 mA/cm<sup>2</sup> of the active electrode surface [25]. There seem to be differing opinions on the effect of the stimulus intensity. However, many authors state that low intensity currents appear to be more effective as a driving force than currents with higher intensities [25]. Therefore, iontophoresis in animals likely could be effective at intensities which would not cause pain or discomfort.

The two **electrodes**, termed the active and dispersive electrodes, are applied to the skin surface. Electrode systems range from simple electrodes fabricated in the clinic to commercially available electrodes specifically made for iontophoresis. Commercially available disposable iontophoresis electrodes include a well that contacts the skin with a semipermeable membrane. Electrode size and shape alter current density and affect the size of the area treated. As a rule, the smaller the electrode, the larger the current density. Choice of electrode size depends on the lesion. When a larger or poorly localized area is to be treated, larger electrodes are indicated.

Frequency of Treatment - This needs to be determined based on the drug chosen and the patient's response.

What About the Hair Coat? - An intact hair coat impedes the penetration of ultrasound waves into the tissues [12]. Whether iontophoresis can be delivered efficiently through an intact hair coat remains to be studied. For human patients, authors typically caution that the skin should be shaved and cleaned in order to ensure maximum contact of the electrodes [25]. In published animal experiments, the hair has been removed and the skin cleaned [26,27].

However, there is reason to be optimistic that iontophoresis could be performed with an intact hair coat. Proper electrical conductivity can be established despite the hair coat for other techniques involving electrical stimulation. For instance, the hair can be parted but does not need to be clipped when applying surface stimulating electrodes for nerve conduction velocity studies in domestic animals. And, electrical impedance is low enough that electroencephalograms can be recorded in dogs and other species with surface recording electrodes without clipping the hair.

Precautions - The most severe complication in humans is an adverse drug reaction. Patients allergic to a medication should not receive this treatment. The second adverse reaction is a skin burn. Burns are more common under the cathode. The incidence of burns has decreased after current-regulated generators became available. Safety features are available that automatically terminate the treatment if impedance rises too quickly or too high. Caution should be used if the skin is damaged (since damaged skin has a lower resistance to the current and a burn may occur more easily) or if the patient has a sensory deficit [25]. Banta pointed out that iontophoresis provides an excellent complication and side-effect profile compared with other methods of delivering dexamethasone [28]. In his study, no complications occurred, including no significant elevation of serum glucose in insulin-dependent diabetics.

Clinical Indications - Currently, iontophoresis is used by physical therapists primarily for (1) the treatment of musculoskeletal inflammatory conditions (bursitis, tendonitis, etc), edema, and, (2) the production of local anesthesia of the skin [29]. Most of the published clinical information on iontophoresis involves the treatment of inflammatory conditions. The goal is to use iontophoresis to concentrate the medication directly into the problem area to achieve more rapid recovery. Lidocaine iontophoresis can produce a local anesthesia of longer duration than topical application but shorter duration than infiltration, which is sufficient to enable suture placement. Lidocaine iontophoresis also has been used for performing myringotomies, where anesthesia of the ear canal and ear drum were obtained [29].

A list of indications for iontophoresis in humans includes [25,30]:

- Allergic rhinitis
- Analgesia
- Burns
- Calcium deposits
- Edema
- Fungi
- Gout
- Herpes infection
- Hyperhidrosis
- Inflammation
- Ischemia
- Muscle spasm
- Open skin lesions
- Reflex sympathetic dystrophy
- Scar tissue
- Tumors

Drugs which have been Administered by Iontophoresis - The candidate drug must be both water and lipid soluble [30]. It must be water soluble to remain ionized in solution and it must be lipid soluble to permeate cell membranes. Direct current will transfer any ions of the appropriate polarity. The drug should be in a solution that contains a limited number of extraneous ions that might compete with it [30]. The list of drugs which can be delivered by iontophoresis includes anti-inflammatories, antibiotics, antivirals, antifungals, sclerolytic agents, local anesthetics, and drugs which promote edema reduction, vasodilation, muscle relaxation, wound healing and calcium resorption.



The positive ions include [25,29-31]:

- 5-fluorouracil
- Acyclovir
- Ara-AMP
- Cefazolin
- Copper (copper sulfate as source)
- Hyaluronidase
- Idoxuridine
- Lidocaine
- Magnesium (magnesium sulfate as source)
- Ticarcillin
- Zinc (zinc oxide as source)

The negative ions include:

- 6-hydroxydopamine
- Acetate (to enhance calcium absorption; acetic acid as source)
- Alpha-methylparatyrosine
- Chloride (sodium chloride as source)
- Ciprofloxacin
- Dexamethasone
- Epinephrine
- Gentamycin
- Iodine
- Ketoconazole
- Salicylate
- Tobramycin
- Vancomycin

Research Findings - Anderson has pointed out that a number of methods for local drug delivery to musculoskeletal tissues in horses are available, but that research is required to document the disposition of the drugs delivered by such methods and to correlate the information with efficacy [32]. In order to determine the role of iontophoresis in clinical medicine, both human and veterinary, there is a need for outcome assessments comparing iontophoresis to parenteral, oral and topical routes of administration. Unfortunately, many clinical trials published on the use of iontophoresis for conditions in humans have not had optimal experimental design. Clinical trials have tended to lack adequate controls, random assignment to treatment groups, or else the relevant treatment parameters have not been reported. In some studies, patients received additional modalities such as therapeutic exercise, heating, electrotherapy, ultrasound, etc, or the patients had various musculoskeletal diagnoses and did not represent a uniform population [30].

In an animal study, iontophoresis was performed (4 - 5 mA, 20 min) on two Rhesus monkeys and there was significant penetration of dexamethasone (but not hydrocortisone) compared to controls [26]. Local tissue concentrations of dexamethasone were higher than would be obtained by systemic therapy and lower than would be obtained by local injection. The authors concluded that the concentrations of steroid recovered in the various tissues were sufficient for clinical anti-inflammatory effects. In sites treated with dexamethasone and lidocaine hydrochloride, the depth of penetration was approximately 1.7 cm. They also found evidence that iontophoresis was concentration independent; electrodes containing 8 mg of drug delivered the same amount as electrodes containing 4 mg of drug. Several studies have been conducted on cases of tendonitis, with varying results. In 30 patients with infrapatellar tendonitis, iontophoresis (dexamethasone and lidocaine) was compared to an established protocol consisting of modalities and transverse friction massage [33]. Patients were assessed with a visual analog pain scale, a functional index questionnaire, rating of tenderness on palpation and number of step-ups needed to elicit pain. The authors concluded that iontophoresis may be more effective in decreasing pain, reducing inflammation and promoting healing. Perron et al., [34] studied acetic acid iontophoresis and ultrasound for the treatment of calcifying tendonitis of the shoulder using a randomized control trial and stratified patients according to the type of lesions seen on radiographs. No significant difference was found between groups. Gudeman et al., [35] investigated whether iontophoresis of dexamethasone in conjunction with other traditional modalities provided more rapid pain relief than traditional modalities alone in patients suffering from plantar fasciitis. He used a



randomized, double blind, placebo-controlled study with treatments given 6 times over 2 weeks. Iontophoresis plus traditional modalities showed greater improvement than traditional modalities alone at the end of the treatment period. However, follow-up at one month indicated that there was no significant difference between the groups. Those results suggested that iontophoresis in conjunction with traditional modalities provides immediate reduction in symptoms and should be considered when more immediate results are needed, for example, in treating athletes.

Kaneps et al., recently investigated the iontophoretic administration of dexamethasone into the tarsocrural joint in horses [62]. The hair was clipped at the sites of electrode attachment. They found that the drug concentration in the synovial fluid was detectable but did not reach therapeutic concentrations. They did not evaluate dexamethasone concentrations in the soft tissues underlying the active electrode.

*The section on Iontophoresis was adapted with permission from Steiss JE. Physical therapy in veterinary medicine: Iontophoresis in horses. Comp Cont Edu Pract Vet 2001; 23:95-99 [56].*



Figure 4. Battery-powered iontophoresis unit with electrodes which are available in a variety of shapes and sizes. (Courtesy of Empi Corporation). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

### 3. Electrical Stimulation

Electrical stimulation can be used in dogs with neurological disorders for the purpose of muscle strengthening, retarding muscle atrophy, muscle re-education, relief of contractures, relief of muscle spasm and trigger points, and pain relief. Electrical stimulation tends to be used in the clinical setting, but not as part of a home program. In the author's experience, most pet owners are reluctant to administer electrical stimulation on a regular basis at home, so compliance is poor.

Equipment varies considerably in price and versatility. Some portable units can be purchased for less than \$500 but have limitations on the output with respect to intensity, frequency, ramping, etc. In certain cases, the portable units could be leased to owners or owners could purchase one for home treatment programs. More elaborate electrical stimulation units are commercially available, which have the capability to deliver a more complete range of the settings indicated in Table 1. Some units combine electrical stimulation and ultrasound to allow the therapist to alternately heat the tissue and deliver electrical stimulation.

Table 1. Some of the purposes for which electrical stimulation could be incorporated into the treatment program, and the typical instrument settings.						
Clinical Application	Type of Current	Mode	Frequency (Hz)	Pulse Duration	Duty Cycle	Intensity
1. Muscle Strengthening	AC or Pulsed	Surged	30-50	10-500 $\mu$ s	1:4 or 1:5	strong motor level
2. Retard Muscle Atrophy	AC or Pulsed	Surged	30-50	20-300 $\mu$ s	1:3 or 1: 5	moderate-strong motor level
3. Facilitation (re-ed; tendon transplant)	AC or Pulsed	Surged	30-50	200-500 $\mu$ s	1:2 or 1: 3	minimal-moderate motor level
4. Range of Motion						
A. Single Motion	AC or Pulsed	Surged	30-50	20-300 $\mu$ s	1:1	minimal-moderate motor level
B. Reciprocal	AC or Pulsed	Surged	30-50	20-300 $\mu$ s	1:1 (Continuous & Reciprocal)	minimal-moderate motor level

5. Relieve Contractures	AC or Pulsed	Surged (slow ramp up & down)	30-50	100-500 $\mu$ s	4:1 or 3:1	moderate-strong motor level
6. Relieve Spasticity						
A. Fatigue	AC or Pulsed	Surged	30-50	200-500 $\mu$ s	1:1, 2:1 or 3:1	moderate-strong motor level
B. Antagonist (Reciprocal Inhibition)	AC or Pulsed	Surged	30-50	200-500 $\mu$ s	1:2 or 1:3	moderate-strong motor level
7. Circulatory Effect						
A. Muscle Pump	AC or Pulsed	Surged or Interrupted/Burst	30-50 or 2-4	20-300 $\mu$ s	1:1 or 1:3	moderate motor level
B. Medical Galvanism	DC	Continuous	N/A	N/A	N/A	low sensory level
(Polarity should be 50% of Rx "+" & 50% of Rx "-" with both pads)						
8. Iontophoresis	DC	Continuous	N/A	N/A	N/A	low/dependent on formula
(Polarity is critical and is determined by polarity of the substance used)						
9. Wound Healing						
A. Continuous DC	DC	Continuous	N/A	N/A	N/A	low sensory or sub-sensory level
(Polarity "-" for bactericidal effect and "+" for stimulation of granulation tissue)						
B. High Volt	Pulsed monophasic	Unknown	100	Preset	N/A	sensory level
10. Pain Relief						
A. Conventional TENS	AC or Pulsed	Continuous	50-100	50-100 $\mu$ s comfortable	N/A	low sensory level
B. Acupuncture-like TENS	AC or Pulsed	Interrupted/Burst	2-4	150-500 $\mu$ s	N/A	strong motor level
C. Brief Intense TENS	AC or Pulsed	Interrupted/Burst	Variable 1-4 or >100	300-500 $\mu$ s	N/A	noxious-little or no motor response

TENS = Transcutaneous Electrical Nerve Stimulation

Modified from D. Lions, PT, University of Alabama, Birmingham, AL, USA.



Figure 5. Electrostimulation for pain relief post-operatively in an orthopedic patient. This dog was treated with high frequency, low intensity stimulation (conventional TENS). (Courtesy of Dr. P. Shealy, Veterinary Specialists of the Southeast, Charleston, SC, USA). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 6. Dual channel (or multichannel) electrical stimulators allow more than one pair of stimulating electrodes to be applied to the dog. The purposes include: (1) Production of interferential current (amplitude modulated beats) for treatment of deep pain; and, (2) Reciprocal or alternating patterns of stimulation in cases where range of motion is restricted in two directions (e.g., flexion and extension). (Courtesy of Dr. P. Shealy, Veterinary Specialists of the Southeast, Charleston, SC, USA). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

#### 4. Therapeutic Exercise

Some of the techniques employed for training agility dogs, dressage horses and human patients can be adapted for therapeutic exercise in rehabilitation programs. Because each animal is an individual, no "cook-book" recommendations can be made. However, the exercise program may include some of the following exercises, for use either in the clinic or as part of a home exercise program after the owners or handler have been instructed on how to perform the exercises.

- Weight shifting
- Step up and step down
- Step over
- Serpentine
- Circles
- Figure 8's
- Transitions (slow-fast-slow walk, walk-trot-walk, etc)
- Leash walking on level and uneven surfaces



Figure 7a. Equipment in a canine rehabilitation clinic can include mini-trampoline, sand box, treadmill, ladder (7a) and dense foam (7b). (Courtesy of C. Schulte, PT, Mission MedVet Rehabilitation Services, KS, USA). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 7b. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 8. Physioballs are available in various sizes. In humans, this equipment is used for exercises to improve muscle strength and balance. However, physioballs may have more limited use in canine rehabilitation. Dogs can be positioned with their thoracic limbs resting on the physioball in order to increase weight bearing on the pelvic limbs. But in the author's opinion, care should be taken to avoid over-extension of the spine (lordosis), which potentially could stress the lumbosacral spine, coxofemoral joints and/or sacro-iliac joints. Other forms of exercise can be used to strengthen the pelvic limbs, e.g., gait transitions and uneven terrain. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 9. Treadmills are available in various sizes for dogs. Treadmills are convenient and allow the trainer to control the exercise with respect to time, speed and gradient. The disadvantage is that treadmills do not simulate normal movement - the ground does not usually move under the dog's feet! Consequently, the pattern of muscle activation may differ when the dog is exercising on a treadmill. Therefore, it is recommended that an exercise program incorporates other exercise in addition to treadmill work. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

#### Warming Up your Dog Before Training Sessions or Competition

A dog which is in the more advanced stages of rehabilitation may be performing strenuous exercises. Warm up exercises should be considered. Warm up can be as simple as walking the dog for about 5 minutes, followed by several minutes of jogging. Even though much research remains to be done, virtually all authorities recommend some form of warm up for the purpose of improving athletic performance and protecting against injury. In other species, it has been documented that the mild increases in body temperature and muscle temperature benefit the musculoskeletal system, the cardiovascular system and enhance temperature regulation to avoid heat stress. Warm up exercise can be incorporated into programs for canine athletes and others for both the prevention of injury and as part of a rehabilitation program. Trainers often say that they do not have time to warm up and cool down their dogs. At competitive events, dogs frequently are taken directly from the truck to the line. In contrast, at horse shows, riders and horses usually are seen exercising in warm up arenas or walking on the grounds. For equine athletes, specific details about warm up routines are available. For example, the warm up for a show jumper involves moderate exercise intensity at an average heart rate of 96 beats per minute [36].

Athletic trainers have written extensively about warm up techniques for human athletes. Even though much research remains to be done, virtually all authorities recommend some form of warm up for the purpose of improving performance and

protecting against injury [37,38]. The purpose of this article is to describe the potential benefits of warm up and cool down for canine athletes, based on what has been written for human and equine athletes and for racing Greyhounds [39].

What Is a Warm Up? - The warm up is a preparation phase before exercise. The purpose of the warm up is to produce a mild increase in body temperature of approximately 1 - 2 degrees F, and thereby improve performance and protect against injury. In human athletes, warming up can include walking, jogging, swimming, and/or mild-to-moderate resistance cycle ergometry [37]. Warm up exercise should not be confused with preliminary cardiovascular conditioning [40], such as roading in Pointers early in the season to increase their level of fitness.

Warm up can be classified as passive and active. In passive warm up, an increase in body temperature is achieved by techniques such as massage, diathermy, ultrasound and heat application [41]. However, this does not significantly increase the blood flow to the working muscles [42], and passive warm up is not used to a great extent.

Active warm up is the easiest way to increase muscle temperature. It is divided into two phases, general and specific [43]. General warm up is a form of loosening up, such as walking followed by jogging/trotting. The effect is to raise core temperature (which can be estimated from measuring rectal temperature), heart rate and respiration rate [43]. Some of the procedures used for horses could be adapted for dogs. Typically, the horse is walked for several minutes, followed by trotting. For horses, warm up is often done on a lunge line or under saddle, or occasionally with a treadmill or hot walker if such equipment is available. For racing Greyhounds, 5 - 10 minutes of brisk walking or jogging prior to racing is recommended [39]. Specific (neuromuscular) warm up is a rehearsal for the activity. This phase mimics the anticipated activity and brings about full range of motion of the joints [41]. Specific warm up is thought to improve skill and coordination. Sports that require accuracy, timing and precise movements tend to benefit from some type of specific preliminary practice [41]. Dogs competing in agility would be candidates for including this phase of the warm up.

Stretching exercises have been part of the traditional warm up [37,43,44]. However, in a recent study, investigators have found that muscle stretching performed during the pre-exercise warm up in adult men did not significantly reduce the risk of exercise-related injury [45]. Instead, they concluded that fitness may be an important, modifiable risk factor. For trainers, the warm up for dogs would certainly be simplified if additional stretching procedures did not need to be incorporated.

Guidelines for Warm Up - The ideal warm up prepares the athlete for subsequent activity without creating fatigue [42,43]. Some trainers state that the ideal warm up for any endurance activity is the same activity but at a lower intensity [37]. More precisely, the goal of warm up is to exercise at a relatively low intensity which is less than 60%  $\text{VO}_2$  max or 70% of the maximal heart rate for less than 15 minutes [42].

For people, the aim of the warm up is to increase their body core temperature 1 - 2 degrees F and the muscle temperature up to 5 degrees F [42]. Experimentally, muscle temperatures can be measured using a needle thermistor inserted into the muscle tissue. However, in the field, a guideline for trainers might be that the rectal temperature should increase by 1 - 2 degrees F in order for the muscle temperature to reach a satisfactory level [44]. Or, the trainer or athlete may simply consider that 5 - 15 minutes of low to moderate intensity exercise should be adequate [43]. If a human athlete is sweating freely in normal climatic conditions, it is assumed that this temperature has been reached [44]. Unfortunately, this particular guideline cannot be applied to dogs.

The intensity and duration of the warm up depend on factors such as the individual athlete, the event, the facilities, and the ambient temperature [42,43]. If the warm up exercise is too strenuous or the duration too long, performance can be impaired by fatigue [42]. Excessive warm up depletes energy stores, causes lactic acid build up, and/or raises body temperature too high [43]. In cold weather, a slightly longer warm up may be required, whereas in hot weather, a shorter or less intense warm up may be appropriate [43]. The level of fitness of the athlete is another factor. An elite human athlete may require 20 - 30 minutes of relatively intense exercise to achieve maximal potential, whereas this would be excessive for an unconditioned novice and would result in exhaustion [44]. Even among individuals near the same level of training, variation exists and needs to be taken into account. For instance, individual horses were found to have different increases in rectal temperature after the same duration of trotting and cantering [43].

The effects of warming up soon wear off [37]. After the warm up is completed, the activity or event should begin within several minutes [41]. This allows recovery from temporary fatigue without losing the beneficial effects of the warm up. For human athletes, it is recommended that the time interval be no longer than 10 minutes [37].

### Why should Athletes Warm Up? -

*A. Musculoskeletal Effects* - Numerous beneficial effects of warm up have been documented for the musculoskeletal system. Greater forces are needed to injure a warm muscle than a cold muscle [41]. With an increase in tissue temperature, collagen and the muscle-tendon junctions are more able to stretch, thereby minimizing trauma [46]. When muscles from rabbits were stretched at 35 degrees C, the muscles could be lengthened approximately 31% before tearing whereas warming to 39 degrees C (103 degrees F) allowed the muscles to be lengthened 35% before tearing [47].

In addition, blood saturation can affect the elasticity of muscle. Cold muscles have low blood saturation and tend to be more susceptible to tears than warm muscles [48]. Increased temperature within muscles promotes vasodilation. A muscle achieves maximum endurance performance when all its blood vessels are maximally dilated [37]. Vasodilation increases blood flow and therefore increases the delivery of oxygen and nutrients to muscle and the removal of waste products [43]. At rest, 15 - 20% of the blood flow supplies the skeletal muscles; after 10 minutes of exercise, the percentage may increase to 70 - 75% [37].

No one has conducted a study to measure the limb temperatures in Retrievers working in cold conditions, such as sub-zero ambient temperatures or ponds covered with ice. The degree of thermal insulation provided by the hair coat is not known. If the temperatures of the limbs do decrease while dogs work in these cold environments, then warm up exercise might be important to minimize the tissue cooling.

Another very important result of increased tissue temperature is increased oxygen delivery to muscles. As temperature increases, hemoglobin releases oxygen from the red blood cells to the tissues more readily. Or, stated another way, the oxy-hemoglobin dissociation curve is shifted to the right [38]. Although considerable effort and expense are spent on finding supplements and other methods to increase the oxygen carrying capacity of hemoglobin and therefore enhance aerobic metabolism, here is a built-in mechanism to achieve this result.

The warm up appears to have the most benefit when athletes compete in high intensity-short duration activities, such as sprinting [43]. This could also be relevant to dogs participating in events such as Schutzhund and agility and field trials, where they may be at risk for muscle strain.

Other effects of warm up on the musculoskeletal system include increased speed of muscle contraction and relaxation [41,42]. In contrast, reaction times are prolonged and muscle excitability is reduced when the tissue temperatures are below normal. Warm up is also associated with an increase in muscle strength as well as speed [48]. Warm up has been reported to improve swimming speed and running speed [48].

*B. Temperature Regulation* - Warm up exercises activate the body's heat dissipating mechanisms. When horses were warmed up before brief high intensity exercise, their temperatures did not rise as high during the subsequent high intensity work and they recovered faster [49]. The investigators in that study speculated that the warm up activated blood flow to the skin, causing an earlier onset of sweating and improved heat removal.

Dogs rely on panting and heat loss through the respiratory system rather than sweating. Therefore, separate studies need to be conducted for dogs to determine if the mild elevations in body temperature achieved during warm up can enhance heat loss through the lungs or nasal cavity. Heat stress is a problem which is becoming more widely recognized in sporting dogs. Retrievers [50] and Pointers [51] sometimes have rectal temperatures approaching 105 - 107 degrees F during exercise, representing a rise in body temperature of 3 degrees F or more. Although most of these dogs appear clinically normal and their rectal temperature declines to normal soon after the activity ceases, some dogs seem to experience heat stress to the extent that their training is impaired.

*C. Cardiovascular Effects* - Sudden strenuous exertion can provoke adverse effects on heart function [37]. In one study, healthy men (n = 44) ran on a treadmill for 10 - 15 seconds without warming up [52]. Electrocardiograms (ECG) were recorded immediately after exercise. Seventy per cent of the men had ECG abnormalities that were indicative of insufficient oxygen supply to the heart muscle due to inadequate coronary blood flow. The abnormalities were not related to their age or fitness level. When the men (n = 22) warmed up by jogging for 2 minutes before treadmill running, only 2 had significant ECG changes.

In addition, blood pressure rises higher when there is no warm up. In the study described above, the average systolic pressure was 168 mmHg after the treadmill run. After the 2 minute warm up, the value was 140. Therefore, warm up reduces the

workload on the heart.

At this time, it is unknown whether dogs have the same responses. Electrocardiograms could be recorded from dogs in a manner similar to the study described above in humans. This type of study would help to determine whether some dogs suffer from cardiac dysfunction if they undertake strenuous exertion without warm up, and whether this could be the explanation for poor performance in some dogs.

**Table 2. Summary of the beneficial effects of warm up.**

- Increased strength
- Increased speed of muscle contraction and relaxation
- Increased muscle flexibility
- Increased oxygen delivery to muscles
- Increased nerve conduction velocity
- Vasodilation (and therefore increased delivery of oxygen and nutrients to muscle)
- Increased rate of muscle enzyme activity (which can increase ATP production)
- Decreased pulmonary blood flow resistance
- Decreased lactic acid concentrations after strenuous exercise
- Decreased oxygen deficit
- Decreased heart rate post-exercise

Cool Down (recovery phase, post-event warm down) - The athlete should be allowed a cool down period consisting of low intensity exercise, such as walking. This low intensity activity is used during the early recovery stage to ensure that blood continues to be circulated from the muscles to enhance the washout of the waste products of muscle metabolism, such as lactic acid, and to dissipate heat, thus shortening the recovery time [37,53]. The post-exercise cool down could mirror the warm up. For example, the cool down could consist of low-intensity sport-specific activities, followed by jogging/trotting, then walking. The time till complete recovery depends on the type and intensity of the exercise. From 10 - 20 minutes is usually considered enough time for cool down [53]. In scientific terms, the intensity of the exercise would be 30 - 65%  $\text{VO}_2$  max [42]. Complete recovery may take several hours [53].

Cooling down after exercise is also important for the cardiovascular system. Cooling down helps to promote venous return to the heart [37]. Abruptly stopping exercise can result in a temporary decrease in venous return, reducing coronary blood flow at a time when heart rate and myocardial oxygen demands are still high. In humans with compromised coronary circulation, this situation can lead to angina pectoris, ECG abnormalities and arrhythmias [37].

**Table 3. Summary of the beneficial effects of post-exercise cool down.**

- Return of heart rate and blood pressure toward resting values
- Increased venous return to the heart
- Increased heat loss
- Increased removal of lactic acid

Future Research - Research on warm up techniques should be aimed at answering several questions. For example, what duration and intensity of warm up are needed to produce an increase in intramuscular temperatures? This question could be answered using methods already established for measuring intramuscular temperatures in dogs [12]. Secondly, do warm up exercises activate the dog's heat dissipating mechanisms, as has been shown in horses? Thirdly, do some dogs experience cardiac dysfunction if they perform strenuous physical exertion without warm up, as has been shown in humans? Could this be the explanation for poor performance in some dogs? And, in the long term, how much will the addition of warm up exercises into training help to prevent injuries or enhance their performance?

*The section on Warming Up your Dog Before Training Sessions or Competition was adapted with permission from Steiss JE.*

## **5. Aquatic Therapy**

Aquatic therapy includes both swimming and other aquatic exercise. Providing aquatic exercise for small breed dogs is relatively easy compared to large breed dogs. Small dogs such as Dachshunds can be lifted into a sink or tub, and easily held for support. A heavier dog which is not ambulatory is much more difficult to transport, and will require a more sophisticated pool. The types of facilities that are used for aquatic therapy include:

- Sinks
- Tubs
- Children's wading pools
- Above ground pools (Figures 10-12)
- Underwater treadmill systems (Figures 14)
- Ponds, lakes and beaches (Figures 16-18)

One of the advantages of an above ground pool is that the dog has room to swim and to play. However, the depth is usually around 3 - 4 feet, which is too deep to walk the dog or perform other types of controlled exercise with the dog standing. It is an advantage to the therapist to be able to work with the dog in an environment where the water level is not above the dog's head, so that the therapist can control the exercise. A dog which is swimming may compensate and not use the affected limb (s) in the desired manner. Above ground pools require regular maintenance of the filtration and chlorination (or bromine) systems.

The advantages of an underwater treadmill system are that the water level can be adjusted to the height of the dog and degree of buoyancy desired. The therapist can quantitate the speed and duration of exercise, and observe the gait through the side walls. In this system, the water is drained at each session. However, the interior surfaces of the underwater treadmill need to be disinfected. One disadvantage of the underwater treadmill system is that the therapist is not able to have the dog perform other types of exercises, such as lateral bending. And, an underwater treadmill may cost 2 - 3 times more than an above ground pool.

The optimal water temperature varies somewhat, depending on the type of patient. Rehabilitation pools for humans are often maintained around 90 - 92 degrees F. Lower temperatures are indicated when dogs are swimming and generating considerable body heat, or when the dog will be staying in the pool for a longer time. Patients with spasticity sometimes improve when the water temperature is lower. In other situations, the recommendation for the water temperature for dogs would be closer to 95 degrees F in order to achieve relaxation of soft tissues. Puppies have been noted to shiver after standing in 95 degree F water for 5 - 10 minutes; therefore, the temperature for them may be increased to a temperature which seems comfortable to the therapist. If there is concern about causing hyperthermia, the dog's rectal temperature can be taken.

In addition to the water temperature, attention should be given to the treatment time. The more debilitated, the shorter the duration should be. Initial treatment times may be as short as a few minutes, and then the duration can be increased considerably as the dog progresses through rehabilitation. Many dogs will have been physically inactive for several weeks or more, and then undergo surgery. It can be assumed that these dogs are deconditioned. Such dogs can easily be fatigued if required to swim. A person who has been laid up with back pain and then undergoes back surgery is deconditioned and would not want to start therapy by being put in a pool over his/her head and told to swim for 20 minutes.

Ideally, the dog's vital signs would be monitored during aquatic exercise. This is seldom done, but the therapist can estimate the degree of exertion in some manner in order to avoid exhaustion. It should be assumed that the exercise has been too strenuous when dogs are so tired that they need extra help getting out of the pool, or when they do not want to move the next day.



Figure 10. Swimming can be used for fitness and conditioning as well as for rehabilitation of neurological and orthopedic patients. (Courtesy of Dr P. Shealy, Veterinary Specialists of the Southeast, Charleston, SC, USA). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -





Figure 11a. Above ground pool (Galaxy Aquatics Inc, Houston TX) viewed from the side, showing ramp (11a) and from above (11b). (Courtesy of Dr P. Shealy, Veterinary Specialists of the Southeast, Charleston, SC, USA). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 11b. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 12a. Another example of an above ground pool (Rio Plastics, Brownsville TX) viewed from the side, showing ramp (12a) and from above (12b). (Courtesy of C. Schulte, PT, Mission MedVet Rehabilitation Services, KS, USA). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 12b. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 13a. Examples of flotation devices for dogs (13a and 13b). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 13b. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 14. Underwater treadmill system (Ferno, Wilmington OH) for rehabilitation of a dog with orthopedic injury. (Courtesy of University of Tennessee, College of Veterinary Medicine, Knoxville, TN, USA.) - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

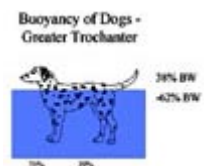


Figure 15. This figure indicates the degree of buoyancy obtained when the water is level with the greater trochanter of the femur. The body weight is reduced by approximately two thirds. (Courtesy of D. Levine, PT, PhD, OCT, University of Tennessee at Chattanooga, TN, USA.) - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 16. A pond is seldom practical for therapy. Many factors such as the water temperature and water quality cannot be controlled. However, in this situation, the therapist can work with the dog to perform a variety of aquatic exercises. This photograph shows weight shifting over the left pelvic limb. The dog's spine is kept straight. Weight shifting is an isometric exercise that is appropriate during the initial rehabilitation of most dogs with either orthopedic or neurological disorders. Weight shifting is usually done with the dog standing on a smooth, non-slippery floor. However, this exercise can be done in water with dogs who are reluctant to bear weight on the affected limb, or who are not allowed full weight bearing. This exercise can be quantitated, for example, "do 10 repetitions and hold for 5 seconds each time". - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -





Figure 17. In addition to weight shifting side to side, as discussed in Figure 16, the dog's center of gravity can be shifted cranially and caudally. This exercise seems to activate the paraspinal muscles as well as the appendicular muscles. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 18. Exercise in water allows unloading of the joints for orthopedic rehabilitation. With neurological disorders, a dog with severe weakness may be able to achieve weight bearing when in an aquatic environment. Where available, a pond or beach with a level bottom allows the dog to be exercised in various heights of water to achieve varying amounts of buoyancy. In addition, equipment such as plastic benches can be used to perform step up exercises in the water (see Figure 19). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 19. Although much of the equipment available for people for aquatic therapy is not readily adapted to dogs, the benches which are seen stacked in this illustration can be placed in water to allow the dog to step up and step down. The degree of weight bearing and difficulty of this exercise will depend on the level of the water and the height of the bench compared to the size of the dog. (Courtesy of Cheryl Fuller, MS, ATC, Aquatics Director, Spain Rehabilitation Center, The University of Alabama at Birmingham). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

What about the possibility of having access to rehabilitation pools such as the one depicted in (Fig. 20) for the purpose of treating canine patients? In many locations, county health regulations prohibit animals in or around these pools (Cheryl Fuller, Director of Aquatic Therapy, Spain Rehabilitation Hospital, UAB, Birmingham AL, personal communication, 2001). Many county health departments allow seeing-eye or care dogs on public pool decks, but do not allow them in the water with their owners (Alison Osinski, PhD, Aquatic Consulting Services, San Diego, CA, 2001).

This question was posed to Dr. Bill Johnston, State Public Health Veterinarian for the Alabama Department of Public Health. He stated that in a properly chlorinated pool, *E. coli* and *Giardia* would be eliminated but *Cryptosporidium* would be a potential concern (personal communication, 2001). Dr. Johnston recommended that the dog be bathed and brushed with a medicated shampoo containing antifungal agents, within 24 hours before entering the pool. The dog should be free of ectoparasites. The veterinarian could perform a fecal screen and even provide a signed health certificate, somewhat similar to the workup for therapy dogs performing hospital visitations.

Dr. Johnston posed this question to members of the National Association of State Public Health Veterinarians, and received the following comments:

- If in contact with the dogs, patients should not have any open or healing wounds.
- The more people in the pool at one time with the dog, the greater the risk of some form of microbe transmission.
- A clear policy is needed on handling fecal and urine contamination of the pool by both dogs and humans.
- Care must be taken to maintain the chlorine concentration at an acceptable level (pool inspection requirements by county health officials state the exact levels of chlorine required to eliminate *E. coli*). There might be concern about patients colonized with multi-drug resistant organisms who may transmit the organism to the dog, which then becomes a source of infection for other patients.
- Even for chlorine sensitive organisms, a certain amount of contact time is needed, since inactivation is not instantaneous.
- *Cryptosporidium* is especially a concern. One should also consider leptospirosis.
- Although *Cryptosporidium* might survive and be infectious if ingested by a person sharing a pool with an infected dog, the degree of risk would not exceed the risk of swimming with a child, for example, a group in which the prevalence of asymptomatic *Cryptosporidiosis* probably exceeds that in most dog populations.
- Humans excreting *Cryptosporidium* and *Giardia* in pools pose more of a potential problem than a healthy clean groomed dog would.



Figure 20. This photograph shows the entrance ramp to a human therapy pool located in a rehabilitation hospital in a metropolitan area. This ramp or beach-type entrance allows easier access for many patients. The water is typically maintained around 92 degrees F. It remains to be seen if therapists in the future will be allowed access to such pools for canine patients. Some of the major issues are concerns regarding control of infectious agents and maintenance of water quality. (Courtesy of Cheryl Fuller, MS, ATC, Aquatics Director, Spain Rehabilitation Center, The University of Alabama at Birmingham). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

## 6. Goniometry

A goniometer is a device which is used to measure joint angles. The therapist places the two arms of the goniometer along the bones immediately proximal and distal to the joint being examined. The two arms of the goniometer are lined up with specific anatomical landmarks for each joint. Goniometry can be used to determine both a particular joint position and the total amount of motion available at a joint [54]. Goniometric measurements are not usually performed if the dog appears to have normal range of motion on physical examination. When goniometry is performed, the animal's limb position should be standardized so that measurements are repeatable on subsequent examinations. In cases where only one limb is affected, the contralateral normal limb can be used for comparison. There is a need for data on the normal ranges for joint angles for individual breeds of dogs. Values for the Labrador Retriever have been reported [63].

Data obtained from goniometry can be helpful in the following circumstances [54]:

- Determining the presence of dysfunction
- Establishing a diagnosis
- Developing treatment goals
- Documenting progress
- Modifying treatment
- Motivating the owner
- Fabricating splints (orthoses)
- Obtaining objective data

## 7. Orthotics

Low temperature thermoplastics are materials that have been utilized for many years in the fabrication of orthotic devices or splints for human use. Due to the versatility of these materials, orthotic fabrication can easily be modified in order to meet the needs of a veterinary practice.

Orthotic devices are used in the human medical model to protect joints against forces that cause pain, injury, deformity or stresses that interfere with the healing process. Orthotics, or splints, are also utilized to correct joint contractures, tendon subluxations, reduce hypertonicity in spastic musculature, and to assist movement of joints during activities when muscle strength is decreased or absent due to nerve injury or paralysis.



Figure 21. Orthotic for a Labrador Retriever with radial nerve damage and knuckling of the paw of the right thoracic limb. (Courtesy of R Johnson, Department of Occupational Therapy, University of Alabama at Birmingham, AL, USA [58]). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Many diagnoses addressed in veterinary practice can be treated with the use of orthotic devices, and due to the characteristics of the materials and ease of molding and remodeling; it can also be of cost benefit. Joint injuries, soft tissue injuries, wounds, tendon lacerations, fractures, nerve injuries, sprains, joint laxity, contractures, and vascular repairs are common diagnoses that can benefit from splint fabrication.

There are different categories of orthotic devices, including static devices, nonarticular (fracture) splints, serial-static and static progressive devices, dynamic splints, and static motion-blocking splints. Static, serial-static, and nonarticular splints can easily be modified for use in the treatment of domestic animals. Static splinting devices are designed to prevent

contractures by maintaining tissue length, resting injured tissues to reduce inflammation and pain, stabilize injured tissues, and reduce muscle tone in the treatment of spasticity. They are also utilized to unload tissues to promote resorption of lax structures such as joint capsules or ligaments in order to correct joint instability, and to position the joints in the extremities to enhance joint alignment and promote pain-free, functional mobility.

Serial-static orthoses immobilize one or more joints and are designed to reduce muscle tone and correct contractures. This is accomplished by applying a gentle, prolonged stretch to enhance the growth of contracted soft tissues. Due to the nature of low temperature thermoplastics (LTTs), the splints can be reheated and remolded to accommodate the changing tissues. Nonarticular splints do not cross any joints and are usually circumferential, which are useful in the stabilization and promotion of healing in long bone fractures.

Characteristic of Low Temperature Thermoplastics (LTTs) - LTTs are materials that are heated in water at a low temperature (150 - 175 degrees F) that can be molded directly on the surface of a client's skin or animal's fur. There are many types of LTTs available on the market, and these materials may differ in appearance, molding characteristics, durability, cost, color, and thickness. The more commonly used materials typically require a temperature of approximately 160 degrees F. When heated, the thermoplastic materials become pliable, allowing the fabricator to contour the material around the extremity or body part. The material then cools and hardens within a few minutes to its original rigidity.

Some materials have **memory**, the quality of returning to original shape when reheated. This is convenient when changing the splint angle frequently, but can pose a problem when spot heating for minor adjustments. **Drapability**, or **conformability**, is the degree to which the heated LTT readily conforms to the contours of the body part over which the material is placed. Although difficult to handle initially, this quality is appreciated when close contouring around bony prominences and tendon insertions is needed. The greater the degree of drape, the less resistant it is to stretch, which may be necessary for lengthening a splint. Some materials have the ability to achieve smoother edges after cooling than others. The better a LTT is in **edge finishing**, the smoother the finished splint will be, and more comfortable the splint will be to the client. If finished edges are rougher than desired, a light adhesive padding material can be added to the splint edges for greater comfort.

Some materials tend to be easily fingerprinted during molding, which gives a less than aesthetically pleasing product. These materials must be monitored closely during the molding stage to ensure that fingerprints are not added, if this is a priority. **Durability** is the quality of a LTT material related to the length of time that a material will last. This characteristic is important to consider when a splint will be worn for long periods of time. **Rigidity** is the ability of a material to have a high degree of strength and resistance to stretch, which is an important quality when fabricating splints for large breed dogs. Some materials are perforated, which allows for better air exchange. This is important to consider in warmer climates and seasons where sweating may cause the client's skin to become macerated. Finally, LTTs come in 1/8, 3/32, and 1/16 inch **thickness**. Lighter weight materials may be used for individual clients who cannot tolerate the weight of thicker materials. Thinner materials are not adequately rigid enough for large splints, but are convenient to use for smaller canine and feline clients.

Fabrication of an Orthotic Device - Unheated LTT splinting material can be cut with a pair of good quality scissors or razor edge. The basic length and width can be approximated and more accurate cutting completed once the material has been heated. A pattern or template can be used and scratched or drawn onto the surface prior to heating. The material is then placed in a water bath at a temperature recommended by the manufacturer of that particular material. Most materials become pliable and are workable at a range of 150 - 165 degrees F. An electric frying pan or hydrocollator may be used; commercially available splinting pans can be purchased that have preset thermostats, which maintain a constant, consistent temperature range. A candy thermometer can be used to accurately monitor the water temperature. Too high a temperature will cause the materials to overstretch and make orthotic fabrication difficult.

Once thoroughly heated (2 - 3 minutes), the pattern can be cut from the material blank. The pattern is then dried with a towel and placed onto the surface of the affected area. The material is smoothed into place, and edges are gently flared to avoid pressure at the splint edges. The splint is then allowed to cool while gently held in place, which usually takes 2 - 3 minutes. The splint is then removed from the animal, and cooled completely by running under a faucet with cold tap water. The edges are then checked for sharp areas, and if any are present, the edge can be gently run through the hot water bath and smoothed without having to completely reheat the entire splint. Velcro loop straps are then cut and sticky-back hook Velcro is placed onto the splint in order to hold it in place. The orthotic device can also be held in place by using tailwrap or Coban wrap over the entire surface. If a wound or surgical site is present, a sterile dressing can be placed onto the affected surface prior to splint construction. The pet's owner should remove the splint and check the skin for signs of pressure after being worn for approximately one hour. The animal should be observed for signs of distress if the splint is causing discomfort. The splint can

be reheated and remolded if needed several times before a new splint is warranted. The splint can be cleaned with a cool soapy cloth and rinsed, or cleansed with a cotton swab and rubbing alcohol. The splint should never be left near open heat or in an automobile on hot days, as the material can warp if exposed to heat.

Case One - A 12 month Himalayan mix cat was found with her right front leg caught in a jaw-type animal trap. The device caused a severe soft tissue injury, causing nerve damage and a resultant foot drop deformity. The nerve was damaged to the extent that a primary repair was not possible. The injury rendered the leg non-ambulatory. A large ulcer formed on the dorsal surface of the tarso-phalangeal region of the damaged lower leg, with the ulcer extending into the peritendinous fascia of the extensor mechanism. The therapist was consulted to assist with wound management by placement of the injured leg in a custom posterior splint to position the foot into dorsiflexion up to a neutral position, therefore impeding weight-bearing onto the dorsal surface. A 5 inch by 1.5 inch section of Polyflex II Light was heated to 160 degrees F and molded over the bandaged posterior leg and foot, bringing the foot into a normal weight-bearing pattern. The splint was held in place with Coban wrap. Upon regaining consciousness, the cat was able to weight bear and assume a relatively functional ambulatory status. Due to proper alignment of the foot, the dorsal surface was no longer utilized as a weight bearing surface and gradual healing of the ulcer took place.

Case Two - Cassidy is a 3 year old mixed breed dog that had been severely neglected. The dog presented with a flexion contracture of the right carpus and digits. Cassidy was referred for splinting to decrease excessive soft tissue tightness that has caused the contracture.

Over a course of 5 months, the dog was seen weekly to bimonthly for custom static progressive splinting to gradually increase dorsiflexion and decrease the flexion contractures present. Throughout the course of treatment, the foot was maintained in a constant state of low, static tension, which allowed the realignment of collagen present in the scar tissues, slowly remodeling of all soft tissues.



Figure 22a. Orthotic for a Labrador Retriever with partial radial nerve damage and subsequent knuckling of the paw (22a). The dog was not able to fully extend its carpus. This splint was worn 10 hr per day with excellent tolerance. The goals were to prevent flexion contracture of the carpus and to prevent skin abrasions. Vetrap was placed over the splint to prevent the splint from slipping (22b). - To view this

image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -



Figure 22b. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

The author thanks Dr. Don Sorjonen for the case referrals.

*The section on Orthotics was adapted with permission from Johnson R. The use of thermoplastic materials for splinting in veterinary practice. Comp Cont Edu Pract Vet 2003; 25:20-28 [58].*

## **8. Exercise Prescriptions**

### **a. Joint Contracture**

Signalment - "Missy", 3 year old F/S Pomeranian.

History - This dog had Cushing's disease. Three months prior, she experienced acute paralysis of the left pelvic limb from a blood clot, which caused ischemic necrosis of muscles (and possibly some nerve fibers) below the stifle. Since that time, she dragged the limb and traumatized the foot. After trying various boots, which either did not fit or tended to wear quickly, the owners found a satisfactory boot which was worn during the day ("Muttluks" [www.muttluks.com](http://www.muttluks.com)).

Presenting Complaint - The owners wanted information on rehabilitation before considering amputation.

Initial PT Evaluation - Abnormalities were restricted to the left pelvic limb. There was severe atrophy of muscles below the stifle, and moderate atrophy of the quadriceps femoris. Passive range of motion (ROM) at the hip was within normal range. Goniometry indicated full extension at the stifle and hock, but flexion was limited to 90 degrees at the stifle and 60 degrees at the hock. With the dog standing, the limb could be placed in a weight bearing position, but she dragged the leg in extension when walking. The medial aspect of the foot was ulcerated and inflamed. The owner stated that the swelling was responding

to antibiotic therapy. Sensation to the limb was intact. The patellar reflex appeared decreased.

#### Short Term Goals -

1. Increase ROM of stifle and hock, left pelvic limb;
2. Strengthen muscles, left pelvic limb;
3. Instruct owners in a home exercise program (HEP).

#### Long Term Goal - Regain normal function of affected limb.

Treatment - The owners were given the following HEP to be done 4x per day. Steps 2 - 4 were demonstrated, including hand placement for the stretching exercises, and the owners practiced under supervision before leaving the clinic.

1. Warming the tissues: Apply moist heat to the LH limb for 5 minutes (towel soaked in warm water or a hot pack, at a temperature which you find tolerable). Alternatively, leash walk x 5 minutes, with boot on, since exercise can also warm up the tissues. Step 1 can be omitted if time does not permit.
2. Stretching: With your dog relaxed in lateral recumbency, affected limb uppermost, bend the stifle to the point of resistance and hold for 20 - 30 sec. If you feel any relaxation or "give" while you are holding, increase the bend till you encounter the new point of resistance. Relax for a few seconds and repeat 2x. Treat the hock joint similarly.
3. Exercise (weight shifting): With your dog standing with all 4 feet positioned normally, her spine straight, place your hands on her left and right flank and shift her weight onto her affected limb. Hold for 10 sec. Repeat 10x.
4. Leash walk for 5 minutes at a speed slow enough that she is able to put weight on her affected leg and place it in the correct position.

Re-evaluation - By 2 weeks, the owners reported that Missy had started jumping onto furniture and occasionally put weight on her affected limb when running. At the 3-week recheck, passive ROM at the stifle was 0 - 120 deg (flexion increased 30 deg) and ROM at the hock was 0 - 85 deg (flexion increased 25 deg). Swelling was absent from the foot. The owners were advised to continue the HEP until ROM in the stifle and hock appeared to be the same as in the unaffected limb. The boot was gradually worn for shorter times each day.

Follow-up - By 10 weeks, the owners estimated that ROM at the stifle had further increased to 150 deg of flexion. She continued to hold the affected limb up when running at top speed. By 20 weeks, the owners stated that she was "back to normal", and consistently ran with "4 on the floor". They continued to perform the stretching exercises once per day. Missy continued to receive Warfarin and Lysodren medication.

Comments - It can be difficult to predict how rapidly contractures will respond to treatment. This dog benefited from the excellent compliance on the part of the family members. For instance, they divided up the therapy so that the person who disliked performing the stretching did the leash walking. Goniometry was helpful to document increased ROM and to provide positive feedback for the owners. For this dog, the Muttluks boot gave enough support and protection to the distal limb so that we did not think that it was necessary to make a custom-fitted splint.

#### **b. Thoraco-lumbar Intervertebral Disk Disease, Non-weight-bearing in Pelvic Limbs**

Signalment - "Rosebud", 7 year old Dachshund, F/S

History - This dog had previously undergone surgery for a herniated intervertebral disk at T13 - L1. The dog had made an uneventful recovery and was ambulatory. Eight months later, the dog experienced a second onset of paraplegia associated with intervertebral disk herniations in the caudal thoracic spine as determined on myelogram. The owner was reluctant to undertake additional surgery. The orthopedic surgeon who had done the initial surgery suggested that the owner pursue physical therapy.

Presenting Complaint - The dog has been unable to bear weight on the pelvic limbs for 7 days.

Physical Therapy Evaluation - Abnormalities were restricted to the pelvic limbs. The dog had pain sensation in both pelvic limbs. The muscle mass was not decreased. Patellar reflexes were mildly increased. The withdrawal response to toe pinching

was poor in both pelvic limbs. When lifted to a standing position, the dog was not able to bear weight on the pelvic limbs. Joint range of motion was within normal range for both pelvic limbs. The dog moved around by using the thoracic limbs and dragging the pelvic limbs.

Short term goals (within 4 weeks) -

1. Strengthen the pelvic limbs so that dog is able to bear weight for a minimum of 10 seconds without assistance when standing in water.
2. Dog will be able to voluntarily flex each pelvic limb in response to toe pinch while standing with assistance.
3. Maintain range of motion within normal limits in pelvic limbs.

Long term goals - Restore function in pelvic limbs so that dog can ambulate independently in the home environment.

Treatment - The owner was provided with a home exercise program that was demonstrated to her in the clinic, and which she practiced under supervision before leaving the clinic. She was instructed to repeat the following exercises 2 - 3 times each day if possible (but only 1 - 2 times for the exercises in water).

1. Place a rubber-backed mat (or non-slippery mat) on your table or counter top. Support her under her abdomen with one hand and support her under her ribs with the other hand. Place her hind feet so that they are in a normal position under her body. For the first exercise, use one hand to gently lift her up under her abdomen so that her feet are just barely touching the mat and then gently lower her very slightly (approximately a centimeter) so that she gets the sensation of bearing some weight on her hind legs. Repeat 10 times.
2. Continue to support Rosebud in the same manner with her feet placed under her body, and gently shift her weight from side-to-side so that she has the sensation of bearing some of her weight on her left side, and then on her right side. Repeat this 10 times also.
3. Have Rosebud lie on her side while you pinch a toe (on the leg that is uppermost) just enough to get her to pull back that leg. Tell her "good girl!" in order to encourage her to do this without having to pinch a lot. Repeat 5 times. Place her on her other side and repeat. Or, simply do this during the day when she is lying on her side. When she gets stronger, you can do the toe pinches with her standing because working against gravity is more difficult and will strengthen the limbs more.
4. Repeat the first 2 exercises in water once or twice per day. Have the water level near the point of her shoulder, about 95 degrees F so it is comfortably warm. After the exercises, continue to support her under her abdomen and chest with your hands so that she can stand in the water for 5 - 10 minutes. Encourage her to take several steps in the water by helping her to advance her feet. Take her out of the water earlier if she seems to become fatigued.

Follow-up - This dog slowly progressed over 4 months to the point where she could walk, with mild ataxia, on level surfaces in the house.

Comments - The rehabilitation program for this dog was based on a combination of partial weight bearing with assisted stepping and aquatic therapy. Standing and walking with assistance in water helped to give the dog proprioceptive sensory feedback from the pelvic limbs. In addition, seeing her dog able to stand in the water provided motivation for the owner at the start of the program. When thinking about rehabilitation, people often think about dogs swimming. However, this dog was deconditioned after the previous surgery and lack of exercise, and would have become easily fatigued if she had been forced to swim at this early stage of the rehabilitation. In addition, she might have compensated in the water by using her thoracic limbs and not necessarily activating the muscles of the pelvic limbs. By having the dog stand in water, instead of swimming, the therapist is able to control the activity in the limbs. Swimming could be considered later in the program when the goal is to promote cardiovascular conditioning.

Water temperature is important. Cooler water temperatures are indicated when dogs are swimming vigorously and generating body heat. In the author's opinion, water temperatures should be around 95 degrees F for therapy. In cases where the dog is not exercising in the water, but just standing, some dogs will start shivering after 5 - 10 minutes. In this case, the water temperature can be increased closer to 100 degrees F (or what feels comfortable to the therapist). If in doubt, the dog's rectal temperature can be measured.

These procedures are quite easy to carry out on a small breed dog. In this instance, the owner was elderly but she was able to perform the home program. The exercises were done with the dog standing on a table and in a utility sink. Working at this height prevented the owner from having to lean over and potentially injure her own back while doing the therapy, as might

have been the case if she had to lean over to work with the dog in a bath tub. Depending on the weight of the dog, more than one person may be required to perform the therapy and additional equipment such as slings and lifts may be needed

### **c. Thoraco-lumbar Intervertebral Disk Disease, Weight-bearing in Pelvic Limbs**

Signalment - "Max", 5 year old Miniature Dachshund, male/neutered.

History - This dog had undergone three previous surgeries for thoracolumbar intervertebral disk herniations. The most recent surgery had taken place 8 weeks prior to presentation

Presenting Complaint - The dog has moderate weakness and spasticity in the pelvic limbs, with prominent kyphosis.

Physical Therapy Evaluation - The abnormalities were restricted to the thoracolumbar spine and pelvic limbs. When standing, the dog had a severe kyphotic posture. Paraspinal muscles in the thoracolumbar region were severely atrophied. The scars from the surgical incisions appeared healed and the skin in those regions was mobile. The pelvic limbs exhibited increased muscle tone, but the dog was able to ambulate with moderate incoordination. Patellar reflexes were increased bilaterally with occasional clonus. Pain sensation was intact in both pelvic limbs, as judged by response to toe pinch. There were no skin abrasions on the pelvic limbs.

#### Short term goals -

1. To maintain normal range of motion in the pelvic limbs.
2. To strengthen the pelvic limb musculature.
3. To strengthen the lower back muscles and resolve the kyphosis.

Long term goals - To enable Max to function independently in the home environment, with minimal gait abnormality in the pelvic limbs.

Treatment - Below is a copy of the exercise program provided to the owners:

This program should take less than 30 minutes each session. You can do the range of motion exercise and weight shifting twice per day and all the other exercises 3 - 4 times per day. If he appears tired, stop and give him a break before you continue.

Week 1	
<b>Range of motion</b>	With Max lying on one side, put one hand under his hind leg for support (the leg on top) and gently bend his leg and straighten it. Repeat 5x each side.
<b>Weight shifting</b>	Stand at his side, place his hind legs under him, and gently lift one hind leg off the ground so he bears more weight on the other hind leg. Hold for a count of 5. Repeat 5x each side. You may need to use one hand to stabilize his trunk.
<b>Step over and step up</b>	Place 3 boards (approx 1" x 1" x 18") or broom or rake handles in a line 2-3 ft apart. Place the plywood sheet (about ½ " height) about 3 ft from the last pole, in line with the boards. Walk Max down this line of obstacles, circle, and come back in the opposite direction. Repeat 5x. Make him walk slowly enough that he does not bunny hop with his hind legs.
<b>Foam</b>	Use a foam pad 1-2" thick and at least 3 ft long. Have Max walk over it 5x.
<b>Transitions</b>	Do slow-fast-slow walk transitions or walk-stop-walk transitions. Do 5 transitions.
<b>Slope</b>	
<b>"Enriched environment"</b>	During the day, place boards, poles, plywood sheets, foam, toys, balls, carpet strips, etc., around the room so Max has to investigate and walk over some of these obstacles. Change the layout daily (move things around) and add a new toy/obstacle every few days if possible.
<b>Walks</b>	Walk on level ground, preferably outside. Start at 20 ft distance total. Do not allow Max to rush.

Week 2	
Range of motion	With Max lying on one side, put one hand under his hind leg for support (the leg on top) and gently bend his leg and straighten it. Repeat 5x each side.
Weight shifting	Stand at his side, place his hind legs under him, and gently lift one hind leg off the ground so he bears more weight on the other hind leg. Hold for a count of 5. Repeat 5x each side. You may need to use one hand to stabilize his trunk.
Step over and step up	Repeat 10x.
Foam	Repeat 5x.
Transitions	Repeat 10 transitions.
Slope	
"Enriched environment"	During the day, place boards, poles, plywood sheets, foam, toys, balls, carpet strips, etc., around the room so Max has to investigate and walk over some of these obstacles. Change the layout daily (move things around) and add a new toy/obstacle every few days if possible.
Walks	Walk 25 ft.
Week 3	
Range of motion	With Max lying on one side, put one hand under his hind leg for support (the leg on top) and gently bend his leg and straighten it. Repeat 5x each side.
Weight shifting	Stand at his side, place his hind legs under him, and gently lift one hind leg off the ground so he bears more weight on the other hind leg. Hold for a count of 5. Repeat 5x each side. You may need to use one hand to stabilize his trunk.
Step over and step up	Repeat 10x and add a second plywood sheet on top of the first one, so height is about 1"
Foam	Repeat 10x.
Transitions	Repeat 10 transitions.
Slope	Do at walk only. Start on week 3. Walk up and down a gentle gradient, about 10 ft length. Repeat 2x.
"Enriched environment"	During the day, place boards, poles, plywood sheets, foam, toys, balls, carpet strips, etc., around the room so Max has to investigate and walk over some of these obstacles. Change the layout daily (move things around) and add a new toy/obstacle every few days if possible.
Walks	Walk 50 ft.
Week 4	
Range of motion	With Max lying on one side, put one hand under his hind leg for support (the leg on top) and gently bend his leg and straighten it. Repeat 5x each side.
Weight shifting	Stand at his side, place his hind legs under him, and gently lift one hind leg off the ground so he bears more weight on the other hind leg. Hold for a count of 5. Repeat 5x each side. You may need to use one hand to stabilize his trunk.
Step over and step up	Repeat 10x.
Foam	Repeat 10x.
Transitions	Repeat 10 transitions.
Slope	Repeat 4x.



<b>"Enriched environment"</b>	During the day, place boards, poles, plywood sheets, foam, toys, balls, carpet strips, etc., around the room so Max has to investigate and walk over some of these obstacles. Change the layout daily (move things around) and add a new toy/obstacle every few days if possible.
<b>Walks</b>	Walk 50 ft.
<b>Week 5</b>	
<b>Range of motion</b>	With Max lying on one side, put one hand under his hind leg for support (the leg on top) and gently bend his leg and straighten it. Repeat 5x each side.
<b>Weight shifting</b>	Stand at his side, place his hind legs under him, and gently lift one hind leg off the ground so he bears more weight on the other hind leg. Hold for a count of 5. Repeat 5x each side. You may need to use one hand to stabilize his trunk.
<b>Step over and step up</b>	Repeat 10x.
<b>Foam</b>	Repeat 10x. Change to a thicker foam if this becomes too easy.
<b>Transitions</b>	Repeat 10 transitions.
<b>Slope</b>	Repeat 5x.
<b>"Enriched environment"</b>	During the day, place boards, poles, plywood sheets, foam, toys, balls, carpet strips, etc., around the room so Max has to investigate and walk over some of these obstacles. Change the layout daily (move things around) and add a new toy/obstacle every few days if possible.
<b>Walks</b>	Walk 100 ft.
<b>Week 6</b>	
<b>Range of motion</b>	With Max lying on one side, put one hand under his hind leg for support (the leg on top) and gently bend his leg and straighten it. Repeat 5x each side.
<b>Weight shifting</b>	Stand at his side, place his hind legs under him, and gently lift one hind leg off the ground so he bears more weight on the other hind leg. Hold for a count of 5. Repeat 5x each side. You may need to use one hand to stabilize his trunk.
<b>Step over and step up</b>	Repeat 10x.
<b>Foam</b>	Repeat 10x. Change to a thicker foam if this becomes too easy.
<b>Transitions</b>	Repeat 10 transitions.
<b>Slope</b>	Repeat 5x.
<b>"Enriched environment"</b>	During the day, place boards, poles, plywood sheets, foam, toys, balls, carpet strips, etc., around the room so Max has to investigate and walk over some of these obstacles. Change the layout daily (move things around) and add a new toy/obstacle every few days if possible.
<b>Walks</b>	Gradually increase distance to tolerance.

Follow-up - This dog gradually improved so that at 4 months follow-up, he was judged to be functioning at a level similar to his condition before his last surgery. The spasticity resolved to the point where it did not interfere significantly with ambulation. Within the first few weeks, his posture improved and the kyphosis had resolved at the time of follow-up.

Comments - The program for this dog was based on a progressive exercise program for muscle strengthening plus providing an enriched environment. Aquatic therapy was not instituted for this dog, but would also have been an appropriate addition. Exercises in water could have included standing, walking, step ups (onto plastic benches, for example) and step overs, if sufficient room were available in the tub or pool for such equipment.

Exposure to an "enriched environment" in laboratory animal models has indicated considerable improvement in function after spinal cord injury. "Enriched environment" refers to placing the animal in surroundings which encourage activity and challenge mobility. Some studies indicate that the animals should not be exposed to the enriched environment too early after injury, but that this form of therapy should be started several weeks after the injury. These findings are based on studies with animal models such as rats and mice, primarily. Future research needs to be done to assess the outcome in dogs receiving this form of therapy.

#### **d. Lumbosacral Disease, Post-operative**

Signalment - "Jack", 4 year old Golden Retriever, male/neutered.

History - The dog had undergone surgery for lumbosacral disease 3 weeks prior to presentation. Surgery consisted of a dorsal laminectomy and facetectomy on the right side. The neurosurgeon found a large amount of fibrous tissue at the lumbosacral junction in the area of the interarcuate ligament, and the sciatic nerve was compressed on the right side at this level. Trigger points were palpable in the paraspinal muscles on the right side at re-evaluation 3 weeks post-operatively. The dog was receiving nutraceuticals but was not receiving anti-inflammatory drugs at the time of presentation.

Presenting Complaint - The dog seems painful when ambulating or when getting up from a lying position.

Physical Therapy Evaluation - The dog was in excellent body condition. On palpation, the dog had several localized areas of muscle spasm and tautness in the paraspinal muscles on the right side, consistent with trigger points. The dog was short strided in the pelvic limbs, worse on the right, and hesitated when asked to bend laterally at a walk or trot.

Short term goals -

1. Strengthen paraspinal muscles in the lumbosacral region.
2. Improve mobility of the spine, particularly lateral bending.

Long Term Goals - Return dog to full mobility and a pain-free condition so that he can continue to function as an active pet.

Treatment - The following home exercise program was given to the owner:

- Do the exercises 2 - 3 times each day. The exercises should take less than 30 minutes. The outdoor leash walk should be either once or twice per day.
- If Jack becomes sore in his hind limbs, discontinue all the exercising for the rest of that day, and start again the next day at the same level if Jack is no longer sore.
- Avoid letting him run loose outside as much as possible. Rather, keep him on leash.
- Avoid letting Jack gain weight. He is in very good condition at present.

Comment	
<b>Weight shifting</b>	Stand at his side after Jack is standing with his feet squarely under him, one hand on each flank. Gently use your hand to push his weight onto one side, as we did in clinic. Then repeat on the opposite side.
<b>Step up - step down</b>	Use a board or plywood square approximately 18" square and about 1 inch high to make Jack step up and then step down. With plywood, you may need to stack 2 sheets on top of each other. Turn in a wide circle and approach from the opposite direction.
<b>Figure 8</b>	Use plastic cones or other markers such as styrofoam cups to mark a figure 8 which has 2 equal circles of 12 - 15 ft diameter. Be sure you lead him in a smooth circle, not a series of straight lines.
<b>Transitions</b>	Slow-fast-slow walk transitions. This is simply a slight change in speed to displace Jack's center of gravity. You can do this during the leash walks.
<b>Incline on driveway</b>	Do at walk only. Find a slight gradient with a smooth surface. Start this week 3.
<b>Leash Walks</b>	Leash walk on level ground with Jack well under control.

Week 1	
Weight shifting	Hold for a count of 5 seconds, and do 5 reps. If he doesn't like doing this at first, then shift his weight but hold it for less than 5 seconds.
Step up - step down	Step up-step down for 10 reps.
Figure 8	Walking, make a figure 8. Do 5 reps.
Transitions	Change speed at the walk (slow-fast-slow) 10 times during leash walks.
Incline on driveway	...
Leash Walks	Start with the distance that the neurosurgeon recommended, 1/8th mile.
Week 2	
Weight shifting	Increase to 10 reps.
Step up - step down	Step up-step down for 10 reps.
Figure 8	Walking, make a figure 8. Do 5 reps.
Transitions	In addition to walk transitions, start doing walk-trot-walk transitions. Do 10 reps.
Incline on driveway	...
Leash Walks	Double the distance.
Week 3	
Weight shifting	Increase to 10 reps.
Step up - step down	Increase height to approx 2 inches. You can use a street curb if it is approximately this height.
Figure 8	Increase to 10 reps.
Transitions	In addition to walk transitions, start doing walk-trot-walk transitions. Do 10 reps.
Incline on driveway	Walk up and back down the slope a distance of approx. 15 ft. Do 3 reps.
Leash Walks	Maintain same distance as week 2.
Week 4	
Weight shifting	Increase to 10 reps.
Step up - step down	Increase height to approx 2 inches. You can use a street curb if it is approximately this height.
Figure 8	Increase to 10 reps.
Transitions	In addition to walk transitions, start doing walk-trot-walk transitions. Do 10 reps.

<b>Incline on driveway</b>	Walk up and back down the slope a distance of approx. 15 ft. Do 3 reps.
<b>Leash Walks</b>	Increase the distance to approximately 3/8th mile.
<b>Week 5</b>	
<b>Weight shifting</b>	Increase to 10 reps
<b>Step up - step down</b>	Increase height to approx 2 inches. You can use a street curb if it is approximately this height.
<b>Figure 8</b>	Decrease circle diameter to approximately 10 ft. Do 10 reps.
<b>Transitions</b>	In addition to walk transitions, start doing walk-trot-walk transitions. Do 10 reps.
<b>Incline on driveway</b>	Increase distance to 20 ft. Do 5 reps.
<b>Leash Walks</b>	Maintain approximately same distance but include some light jogging during the walk.
<b>Week 6</b>	
<b>Weight shifting</b>	Increase to 10 reps.
<b>Step up - step down</b>	Increase height to approx 2 inches. You can use a street curb if it is approximately this height.
<b>Figure 8</b>	Increase to 10 reps.
<b>Transitions</b>	In addition to walk transitions, start doing walk-trot-walk transitions. Do 10 reps.
<b>Incline on driveway</b>	Walk up and back down the slope a distance of approx. 15 ft. Do 3 reps.
<b>Leash Walks</b>	Vary the walk by including more uneven terrain.

Follow-up - At follow-up at 3 months, the owner stated that this dog had returned to normal function and appeared to be pain-free.

Comments - The rehabilitation in this dog was based entirely on progressive exercise. The weight shifting allowed relatively gentle isometric exercise, which was followed with other exercises on a straight line, such as leash walking, step up-step down, and gait transitions. Lateral bending was achieved with figure eight exercises. If the dog had exhibited more discomfort, lateral bending could have been introduced with serpentines, to achieve mild lateral bending, before asking the dog to walk full circles or figure eight's. In addition, the dog was challenged to accommodate for changes in his center of gravity by working him on leash doing transitions, then short distances on a gradient and later introducing uneven ground. The presence of trigger points in the paraspinal muscles of the lumbosacral region was consistent with chronic pain in that area. Trigger points can serve as diagnostic points. A decision can be made of whether to treat them, using techniques such as manual therapy, needling, or electrostimulation. In this case, the therapeutic exercise program was aimed at treating the primary problem. If the dog had not improved, then the trigger points could have been treated directly. This protocol is an example of how the rehabilitation program can comply with the instructions that the owners receive from the referring veterinarian. In this case, the neurosurgeon had instructed them to start leash walking, and this was incorporated as part of the exercise program.

#### **e. Anterior Cruciate Ligament Rupture, Post-operative**

Signalment - "Sydney", 2 year old, Australian Shepherd, male/neutered.

History - This dog suffered a ruptured ACL when hit by a car on 4/21. His first surgical repair, which was an extracapsular repair, done on 4/30. After discharge, the dog jumped over a barricade at home. The repair was noted to have failed soon afterward. A second surgical repair was performed on 5/24 and the owner kept the dog kenneled at the orthopedic clinic for the following 2 weeks. She presented her dog for physical therapy evaluation on 6/25.

Presenting Complaint - The owner stated that her dog was not putting weight on his operated limb when he walked, instead just touching down with his toes. The owner stated that the only thing she knew to do when her dog returned home was to keep him in a crate and pen, and that she did not know how much activity was too much or not enough!

Physical Therapy Evaluation - The dog was overweight. Physical therapy abnormalities were restricted to the operated right pelvic limb. The dog had moderate - severe muscle atrophy in all major muscle groups of the operated limb. He avoided full weight bearing on that limb, tending to just touch down with his toes. Range of motion of all joints appeared to be within normal limits. Flexion at the stifle appeared mildly restricted due to soft tissue swelling around the joint rather than soft tissue contracture. Goniometry was not performed.

#### Short Term Goals

1. 1. Increase amount of weight bearing on operated limb using progressive exercise.
2. 2. Strengthen operated limb and reverse muscle atrophy associated with disuse.
3. 3. Provide a rehabilitation program that can be performed by the owner at home and which fits within the budget constraints of the owner.

Long Term Goals - Restore mobility, strength and coordination in pelvic limb to enable dog to function as a physically active pet.

Treatment - A home exercise program was explained to the owner and practiced under supervision in the clinic. The exercises were done 2 - 3 times per day. Exercises were done on leash, under control, on level, non-slippery surfaces in the house or outside on pavement. The owner was also advised regarding weight loss in this dog and the additional orthopedic stress associated with obesity.

Comment	
<b>Weight shifting</b>	Stand at his side, one hand over each flank, and gently use your hand to push his weight onto the side of the operated leg, as we practiced in the clinic.
<b>Step up - step down</b>	Use a plywood square about ½ inch high x 24" x 24".
<b>Figure 8</b>	Use markers (cones, Styrofoam cups, etc) to mark a figure eight having 2 circles of equal size (approx 15 ft diameter). Start week 3.
<b>Transitions</b>	Slow-fast-slow walk transitions. This is simply a slight change in speed. You can do this during his leash walks, starting at week 2.
<b>Incline on driveway</b>	Do at walk only. Find a slight gradient with a smooth surface (paved driveway or sidewalk). Start this at week 4.
<b>Leash Walks</b>	Walk on level ground. Avoid lawns for first few weeks since the surface is uneven.
Week 1	
<b>Weight shifting</b>	Hold for 5 sec, x 5 reps. If he doesn't like doing this at first, shift his weight but do not hold it for a count of 5.
<b>Step up - step down</b>	Put plywood on a level surface. Walk straight toward the obstacle. Step up-step down onto plywood. Circle around and repeat 10 x.
<b>Figure 8</b>	...
<b>Transitions</b>	...

<b>Incline on driveway</b>	...
<b>Leash Walks</b>	Walk total distance of 20 ft.
<b>Week 2</b>	
<b>Weight shifting</b>	Increase to 10 reps.
<b>Step up - step down</b>	Put plywood on a level surface. Walk straight toward the obstacle. Step up-step down onto plywood. Circle around and repeat 10 x.
<b>Figure 8</b>	...
<b>Transitions</b>	Change speed (slow-fast-slow) 5 times during leash walk.
<b>Incline on driveway</b>	...
<b>Leash Walks</b>	Increase to 30 ft.
<b>Week 3</b>	
<b>Weight shifting</b>	Increase to 10 reps.
<b>Step up - step down</b>	Increase height to $\frac{3}{4}$ -1 inch.
<b>Figure 8</b>	Walking, make a figure 8 x 5 reps.
<b>Transitions</b>	Change speed (slow-fast-slow) 5 times during leash walk.
<b>Incline on driveway</b>	...
<b>Leash Walks</b>	Increase to 50 ft.
<b>Week 4</b>	
<b>Weight shifting</b>	Increase to 10 reps.
<b>Step up - step down</b>	Increase height to $\frac{3}{4}$ -1 inch.
<b>Figure 8</b>	Walking, make a figure 8 x 5 reps.
<b>Transitions</b>	Increase to 10 transitions.
<b>Incline on driveway</b>	Walk up and back down the slope a distance of approx. 10 ft, x 3 reps.
<b>Leash Walks</b>	Increase to 100 ft.
<b>Week 5</b>	
<b>Weight shifting</b>	Increase to 10 reps.
<b>Step up - step down</b>	Increase height to 2"

<b>Figure 8</b>	Decrease circle diameter to approx 10 ft. Do 5 reps.
<b>Transitions</b>	Increase to 10 transitions.
<b>Incline on driveway</b>	Increase distance to 15 ft, x 5 reps.
<b>Leash Walks</b>	Increase to 5-10 min, or what seems comfortable to him.
<b>Week 6</b>	
<b>Weight shifting</b>	Increase to 10 reps.
<b>Step up - step down</b>	Increase height to 2"
<b>Figure 8</b>	Decrease circle diameter to approx 10 ft. Do 5 reps.
<b>Transitions</b>	Add walk-trot-walk transitions, 5 times, during leash walk.
<b>Incline on driveway</b>	Increase distance to 15 ft, x 5 reps.
<b>Leash Walks</b>	Increase to 5-10 min, or what seems comfortable to him.

Follow-up - Three weeks later, the owner stated that the weight shifting exercise was difficult because Sydney continued to avoid putting weight on the operated limb while standing. However, he did bear weight on the limb when performing step ups and during leash walks. The owner also noted that her dog seemed worn out by the time they were through the exercises, which is consistent with the deconditioning that would have occurred after the length of time that the dog was required to rest. Follow-up at 6 months indicated that the dog was physically active and the lameness had resolved.

Comments - This program is one example of a method for post-operative rehabilitation of dogs after anterior cruciate ligament repair. Rehabilitation can be started within the first few days after surgery, in the clinic, and may incorporate modalities such as therapeutic ultrasound, and electrical stimulation, and underwater treadmill work. The rehabilitation program described here is very conservative, but it was tailored to the client's circumstances. The client wanted to pursue physical therapy after her dog was discharged by the orthopedic surgeon. In the area where the client lived, there were no veterinary rehabilitation facilities available. This owner was very compliant and was happy to be actively involved in her dog's recovery.

According to some rehabilitation specialists, exercises to strengthen the knee extensors have shifted away from open kinetic chain (ie, the distal segment of the limb is not fixated) and toward closed kinetic chain exercises (ie, the distal segment of the limb is fixated) in the rehabilitation of ACL reconstruction in humans. The exercise program for this dog consisted of functional movements which would be classified as closed chain exercises. The goals in ACL rehabilitation include restoration of: the optimal muscle firing pattern, joint stability, and the ability to perform complex movements and skills, while minimizing joint forces. The level of sophistication of the rehabilitation program depends in part on the dog and owner. For performance dogs, additional rehabilitation in the form of a neuromuscular training program could be instituted, for example. In such cases, the rehabilitation could include balance exercises, dynamic joint stability exercises, jumping, plyometrics, and agility exercises followed by specific training in the sport or work to which the dog is returning. The weight shifting exercise is a relatively gentle isometric exercise, but was the most difficult part of the program for this dog. Initially, the dog would not put full weight on the operated limb during this exercise. Within a few weeks, the dog would put weight on the limb, but only if allowed to put the foot in the position he chose, not where the owner placed the foot. During step up's and leash walks outside, he was more willing to bear weight on the limb. To encourage him, the owner occasionally used treats to coax him to perform the step up's.

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## **Radiation Therapy** (26-Mar-2003)

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### **Introduction**

Radiation therapy for tumors of the central nervous system in dogs and cats is a viable treatment option. The availability of radiotherapy has increased with the advent of the veterinary specialty of radiation oncology, resident training programs in this specialty, and University and referral practices offering this treatment modality. Veterinary patients may not be cured of their disease, but will have an increased length and quality of life.

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### **Principles of Radiation Therapy**

**Process of Radiotherapy** - Radiotherapy is a clinical treatment modality where ionizing radiation is used to treat patients with malignant neoplasms. The goal of radiation therapy is to deliver a measured dose of radiation to a defined volume with minimal damage to surrounding normal tissue, resulting in eradication of the tumor. Radiotherapy is generally given in divided doses or fractionated. Radiotherapy is useful in the treatment of localized tumors and can provide long-term local control with preservation of regional function. There are several principles that dictate the prescription of irradiation and therefore the management of cancer patients.

- Tumor staging. Complete evaluation of the full extent of the tumor, which may include multiple imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, and radiography
- Knowledge of the biologic behavior of specific tumor types. This includes potential areas of metastasis that may dictate elective irradiation of lymphatics.
- Defining the goal of therapy: Curative versus palliative treatment.
  - Curative, it is projected that the patient has the probability for long-term survival.
  - Palliative, patient survival for an extended period is not projected. However, irradiation of the tumor will improve the patient's quality of life.
- Selecting an appropriate treatment course, which may include irradiation alone or in combination with surgery and or chemotherapy.
- Determination of the irradiation dose and volume to be treated. This depends upon the anatomic location, histological type, tumor stage, potential lymph node involvement, other tumor characteristics and normal structures present in the area to be irradiated.
- Evaluation of the patient's general condition.

Radiation Doses and Volumes - Different doses of radiation are needed for tumor control, depending on the type and initial number of clonogenic cells present. Clonogenic cells are capable of producing a copy or clone. If these cells are malignant a tumor is generated or regenerated. For example, larger doses are needed to eradicate a 2 cm tumor volume as compared to microscopic disease that may be present after incomplete surgical resection. A clinical tumor can comprise several compartments: macroscopic (visible or palpable), micro-extensions into adjacent tissues, and subclinical disease which is presumed to be present, but not detectable. Radiotherapy treatment portals must adequately encompass all three compartments plus a margin to compensate for geometric inaccuracies during the treatment period. Geometric inaccuracies are divided into inherent mechanical imprecision in the treatment machine and those related to defining the target. The latter includes target determination, target localization and reproducibility of patient positioning at each treatment.

Defined volumes in radiotherapy treatment planning include the gross tumor volume (GTV), the clinical target volume (CTV), and the planning target volume (PTV) [1]. The GTV is defined as all known gross disease including affected lymph nodes. The CTV includes the GTV plus a margin for suspected microscopic tumor extension. The PTV provides a margin around the CTV to compensate for variation in daily treatment set-up or other anatomic movement such as breathing.

Radiation doses are measured in units of absorbed dose, Gray (Gy). A Gray is equal to 1 J/kg energy absorbed in tissue. In general, radiation doses are given in daily, smaller fractions (Monday through Friday) to achieve the desired total dose over several weeks. Examples of fractionation schemes in veterinary radiation oncology include daily 3 - 3.2 Gy fractions for 15 - 16 treatments for a total dose of 48 Gy and 2.5 Gy daily fractions for 18 treatments for a total dose 45 Gy.

### **Radiobiology**

Radiation Damage and Cell Kill - Ionizing radiation kills cells by interacting with critical cellular molecules, such as deoxyribonucleic acid (DNA). The interaction of ionizing radiation with the molecular infrastructure of the cell results in chemical reactions. Damage to the DNA is either direct (DNA strand cleavage) or indirect, mediated by free radicals. Most cells die a reproductive death after irradiation and will therefore die at a rate consistent with the cell cycle duration. Slowly proliferating tissues respond slowly, whereas rapidly proliferating tissues and most tumors respond more quickly. There are many factors that influence the radiation response of cells in normal tissues and tumors. Some important factors that account for radioresponsiveness are the number of clonogenic cells, redistribution or reassortment of cells in the cell cycle, repair of radiation injury, repopulation by stem cells, and the oxygenation status.

Proliferating cells are more radiosensitive and have a greater cell loss/turnover rate. Normal tissues and tumors that are rapidly proliferating are more likely to be irradiated at the radiosensitive phase of the cell cycle. Cells are most sensitive to ionizing radiation during M (mitosis) and G2 phases of the cell cycle and most resistant in late S phase (DNA synthesis). The redistribution or reassortment of cells in the cell cycle is one reason behind fractionation of the radiotherapy dose. Dividing the radiation dose into multiple fractions allows cells to reassort to more sensitive phases of the cell cycle before the next treatment.

Almost all tumor cell lines undergo some repair of sublethal and potentially lethal radiation damage [2]. Repair of radiation damage will decrease tumor control, but increases normal tissue tolerance. Hence, another reason the radiation dose is fractionated is because normal tissues are included in the radiotherapy field. Cells of normal tissues are killed by ionizing radiation and time needs to be allotted for their repair and repopulation. Repopulation of stem cells will decrease tumor control, but increases normal tissue tolerance.

The oxygen status of the tissue undergoing irradiation affects radiosensitivity. The presence of oxygen is necessary to fix or make permanent DNA damage mediated by free radicals. When oxygen is absent, three times as much radiation is required to produce the same effect as when tissues are fully oxygenated [3]. Many tumors are known to contain foci of cells that are hypoxic because of their distance from capillaries. During the course of radiation treatment oxygenated cells close to capillaries may be killed, allowing oxygen to reach previously hypoxic cells (reoxygenation), thereby increasing their radiosensitivity [3]. Less responsive tumors are thought to have a high percentage of hypoxic cells or a lower rate of reoxygenation [4].

Normal Tissue and Tumor Response to Radiation - After clinical doses of ionizing radiation, cell death typically occurs at the next attempt of mitotic division [5,6]. Therefore, the time to development of most normal tissue injury depends on the cell turnover rate of the tissue in question. Acute responses to radiation are seen in tissues with a high rate of cell turnover. Examples include gastrointestinal mucosa, bone marrow, skin, oropharyngeal and esophageal mucosa. Hierarchical cell populations exist in these tissues consisting of stem cells, progenitor cells, and highly differentiated mature functional cells

[7]. Ionizing radiation depletes the stem and progenitor cell pools. Function is maintained until the differentiated cell pool is depleted due to normal cell loss and will not be restored until the stem and progenitor cell pools are replenished. Late effects of radiation therapy can be considered as secondary to depletion of slowly proliferating cells. Examples of tissues with a slow rate of cell loss include nervous tissue, kidneys, blood vessels, fibroblasts in the dermis and bones. In contrast to acutely responding tissues, slowly proliferating tissues have both functional and proliferating roles; they are considered flexible rather than hierarchical [7]. Late effects are much more dependent on the dose size and the time since exposure to radiation. Acute effects are relatively independent of dose and determined more by the normal and rapid rate of differentiated cell loss [8]. In general, most tumors respond to radiation like acutely responding tissues.

Tissue repair of radiation injury can occur when a dose of radiation is fractionated into several smaller doses rather than delivered in one large dose. Fractionation of radiation doses will spare slowly responding normal tissues and works to a slight disadvantage for tumor control. Slowly responding tissues have a greater capacity for tissue repair than rapidly responding tissue and fortunately most tumors are rapidly responding. Tissue repair and the sparing of slowly responding normal tissues is the reason that most radiation therapy is delivered in multiple small fractions over 3 to 6 weeks.

### **Technology and Equipment**

Treatment of tumors with radiotherapy involves the use of external beam radiotherapy machines or brachytherapy.

Brachytherapy involves the placement of sealed radioactive sources into or directly adjacent to the tumor. External beam radiotherapy machines include orthovoltage units, linear accelerators, and machines using isotopes.

Brachytherapy - An advantage of brachytherapy is that high doses can be delivered locally to the tumor in a short period of time with low doses in the surrounding normal tissue. Isotopes used in brachytherapy can be embedded in a surface applicator, which is directly placed on the tumor. Surface applicators are used for superficial tumors; the maximum dose is at the surface and falls off rapidly with depth. Isotopes can be sealed into seeds, needles or tubes that are placed into body cavities (intracavitary), tubular organs (intraluminal), or directly through the tumor (interstitial). With all of these methods the radioactivity is sealed inside a shell to prevent leakage of radioactivity into tissues. Today the most commonly used isotope is Iridium-192, which emits gamma radiation with an average energy of 0.380 million-electron volts (MeV). Isotopes used in brachytherapy are implanted in the patient for a limited period of time until the desired dose is delivered and then removed.

Orthovoltage units - Orthovoltage units are relatively low energy external beam radiotherapy machines, x-ray machines operating in the range of 150 - 500 kilovolts peak (kVp). In a typical orthovoltage beam, the maximum dose is at the skin surface and falls to 90% at approximately 2 cm of depth. Due to this dose drop off, it is difficult to treat deeply seated tumors without causing severe skin reactions.

Linear Accelerators - Linear accelerators are external beam radiotherapy machines that use high-frequency electromagnetic waves to accelerate electrons to high energies. The electrons can be extracted to treat superficial tumors or directed to strike a target to produce high-energy x-rays used to treat deep-seated tumors. There is increased flexibility with linear accelerators where lower energy electrons can be used to treat superficial skin tumors and higher energy x-rays used to treat deeper tumors with a lower dose to the skin.

External Beam Radiotherapy Machines using Isotopes - External beam radiotherapy machines using isotopes include cobalt-60 (Fig. 1) and cesium-137. Because isotope machines are constantly emitting radiation they need to be shielded when in the "off" position. When the machine is in the "on" position, the isotope source is moved to an unshielded window allowing the radiation to be directed at the patient. The cobalt-60 source decays over time with a half-life of 5.26 years, emitting gamma radiation with an average energy of 1.2 MeV. Like the higher energy x-ray beam from a linear accelerator there is also a skin sparing benefit with cobalt-60 treatment; the maximum dose is beneath the skin surface. The relatively high penetrability of cobalt-60 makes it a good isotope for teletherapy. In contrast, cesium-137 has lower gamma ray energy of 0.662 MeV and few cesium machines are still in use.



Figure 1. Isocentric Cobalt-60 external beam radiotherapy therapy machine. The letter "A" is located on the source head. This houses the radioactive source, which is shielded in the "off" position and moved to an unshielded opening in the "on" position for patient irradiation. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

**Advanced Technology** - Advances in machinery and computers have resulted in more precise treatments, targeting the tumor volume and reducing dose to normal tissues. The development of intensity-modulated radiotherapy (IMRT) through the application of 3D treatment planning and multileaf collimators (MLCs) has achieved this goal of improving the therapeutic ratio. IMRT is a 3D conformal radiotherapy technique where treatment beams are spatially and temporally modulated to maximize dose to the tumor volume, while minimizing dose to normal structures. Newer linear accelerators permit more control over the shape of the treatment beam with the use of a MLC, which allows shaping of the treatment field to conform to the contour of the tumor. The MLC has 20 to 80 movable leaves, or shields, that can block some fraction of the radiation beam and allow shaping of the field [9]. This has led to the development of helical tomotherapy, which is the combination of a linear accelerator with a MLC and a helical CT gantry (Fig. 2). The integration of CT capabilities and IMRT into one unit makes tomotherapy a closed loop for planning, delivery and verification in radiotherapy [10]. The first clinical tomotherapy unit has been installed at the University of Wisconsin and is undergoing testing. Dogs with spontaneously arising nasal tumors will be the first patients treated on this unit and the conformal avoidance capabilities of helical tomotherapy will be investigated. With this new technology the nasal tumor can be effectively treated while avoiding excessive dosage to the eyes. The goal in treatment advancements is to effectively and accurately treat the tumor while minimizing radiation effects on surrounding normal tissues, thus improving the therapeutic ratio.



Figure 2. Tomotherapy Unit. This radiotherapy unit combines a 6 MV linear accelerator with a helical CT gantry. This combination of technologies provides accurate treatment set-up verification with on-line imaging, and dose delivery verification during treatment. (Courtesy of TomoTherapy, Inc., Madison, WI, USA). - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

Another highly technical treatment is stereotactic radiotherapy. This involves focal irradiation using high doses to stereotactically localized lesions. The requirements for positional accuracy of radiation dose delivery are even more rigorous in stereotactic irradiation than in standard radiotherapy because high doses are given to small lesions in proximity to vital radiosensitive structures [11]. Stereotactic irradiation techniques are most often applied to intracranial structures since the cranium lends itself to the stable fixation of stereotactic frames rigidly attached to the patient. These stereotactic frames allow accurate determination of spatial coordinates of any point within the organ. These coordinates are used to direct external beam radiation to the target volume [11]. Although most veterinary patients are treated with external beam radiation using either a linear accelerator or Cobalt-60 unit, the veterinary radiation oncology community is maintaining a progressive profile. In a recently reported study of radiosurgery using a stereotactic headframe system to irradiate 3 dogs with brain tumors, survival times were 56, 66 and 227 weeks [12]. Using a stereotactic headframe and CT localization the brain tumors were targeted with non-coplanar stereotactically focused beams of radiation in a series of arcs to deliver a single dose of 10 - 15 Gy with great accuracy [12].

Stereotactic irradiation, IMRT techniques and other innovative advances in radiotherapy such as tomotherapy are highly computer driven and require a large number of personnel for treatment planning and delivery. Therefore, these techniques are limited to institutions that employ medical physicists, dosimetrists (involved in radiation computer treatment planning) and computer personnel in addition to radiation oncologists and radiation therapy technologists.

### **Radiotherapy of the Central Nervous System**

**Neural Cell Response to Radiation** - Normal cells in the brain and spinal cord are either static or slowly dividing. Because of this, radiation effects on brain tissue are primarily delayed reactions with little dose-limiting acute toxicity other than edema. Because the central nervous system (CNS) is a late-reacting tissue, normal CNS parenchyma is sensitive to the size of individual radiation doses (dose per fraction). There is a large capacity for sublethal and potentially lethal damage repair of neural tissue at lower doses per fraction. Tumor cells have diminished capacity for sublethal damage repair; therefore, there is less sparing of tumor cells as compared to normal neural tissue with smaller fraction sizes. A large percentage of tumor cells are actively dividing and will reassort into radiosensitive phases of the cell cycle between daily fractions of radiation, thus further increasing the therapeutic differential.

**Radiotherapy Protocols** - In human medicine, primary CNS tumors are treated with external beam radiotherapy to a total dose of 50 to 60 Gy in 25 to 30 fractions delivered over 5 to 6 weeks [13]. Due to the difficulties involved with required daily anesthesia and increased cost, most veterinary patients are treated with a lower total dose and fewer fractions. Treatment regimens for CNS irradiation reported in the veterinary literature vary from total doses of 30 - 54 Gy in 2.4 - 9 Gy fractions

[14-26,52,53]. Due to the fact that neural tissue is late-responding in terms of radiation effects, multiple fractions of 3 Gy or less should be used. With this fractionation schedule, the tolerance dose of normal CNS tissue is 50 - 55 Gy [27]. At the University of Wisconsin, School of Veterinary Medicine the neural tissue protocol is 45 Gy given in 18, 2.5 Gy fractions Monday through Friday over a 4-week period.

### Radiotherapy of Brain Lesions

**Basic Principles and Techniques** - Delivery of radiotherapy to the brain can be accomplished with fractionated external beam irradiation, stereotactic irradiation, and interstitial implantation of radioactive sources. In veterinary medicine, radiotherapy is used to treat tumors and non-neoplastic processes and is generally delivered by fractionated external beam irradiation.

Megavoltage (Cobalt-60, linear accelerator) irradiation is preferred over orthovoltage radiation as the latter has poor beam penetration, inconsistent energy absorption, and limited radiation portal configuration. Computer based radiation treatment plans are preferred allowing accurate targeting of the intracranial lesion and improved target dose distribution.

Intracranial masses in dogs and cats most often have presumptive diagnoses based on the computed tomographic (CT) and magnetic resonance (MR) characteristics [28-30]. Histopathologic diagnosis is often not pursued prior to treatment with radiation therapy and a presumptive neoplastic classification is based on mass location and contrast enhancement on CT or MR imaging (see Brain tumors). Masses in a peripheral location with marked contrast enhancement are considered meningiomas, intra-axial location with poor or heterogeneous contrast enhancement are consistent with tumors of glial origin, contrast enhancing masses at the level of the sella turcica are deemed pituitary tumors, and enhancing masses of choroid plexus location are regarded as choroid plexus tumors [25,28-30].

**Radiotherapy of Brain Tumors** - In the few reports in the literature of veterinary patients with intracranial lesions treated with radiotherapy, it has been shown to be an effective treatment [14-17,20,22,24,25,31,52,53]. Reported median survival times in dogs with brain tumors following radiation therapy alone range from 150 - 360 days [14,16,17,23,25,31] and is better for dogs with pituitary tumors and mild neurologic signs [15,22]. Table 1 and Table 2 summarize the reports in the veterinary literature of radiation therapy for intracranial masses and pituitary tumors. Patient numbers in these studies are small, making it difficult to determine the radioresponsiveness of particular tumor types. The most common intracranial tumors in dogs are meningiomas and gliomas (astrocytoma, oligodendroglioma); meningiomas are the most common tumors in cats [27] (see Neoplasia of the nervous system). Generally, intracranial tumors do not metastasize and local control is beneficial [27].

Table 1. Summary of reports of radiation therapy for dogs with intracranial masses.					
Authors	No. Dogs	Radiation Source *	Total Dose	Protocol **	Median Survival (wks)
Turrel, et al.	4	Cobalt-60	36 Gy	6 Gy x 6 fx	46
Heidner, et al.	25	Cobalt-60	45.6 - 48 Gy	3.8 - 4 Gy x 12 fx	20
Evans, et al.	9 5	240 kV 240 kV	39 Gy 45 Gy	3.25 - 3.75 Gy x 12 fx	19 32
Norman, et al.	47 26	Modified CT-140 kV	Median-34 Gy Median-39 Gy	5.6 Gy x 1 - 15 fx	19 32
Spugini, et al.	29	Cobalt-60	48 - 54 Gy	3 Gy x 16 fx	35.7
Brearly, et al.	83	4 MV linac	38 Gy	Wkly fx 5,7,8,9,9 Gy	43.7
Theon, et al.	20	Cobalt-60	48 Gy	4 Gy x 12 fx All post-surgery	Not reported ‡PFS= 120±36
Axlund, et al.	12	Cobalt-60 6 MV Linac	28 - 49.5 Gy	Not reported All post-surgery	66

\*Radiation sources are external beam and include megavoltage machines, Cobalt-60 and linear accelerators (linac) and lower energy machines, orthovoltage (250 kV) and a modified CT scanner (modified CT-140 kV).

\*\*Radiation protocols are described in terms of dose per fraction (Gy) times the total number of fractions (fx) given.

‡PSF refers to the median (± SE) duration of progression free survival in weeks.



Table 2. Summary of Reports of Radiation Therapy for Dogs with Pituitary Tumors.					
Authors	No. Dogs	Radiation Source *	Total Dose	Protocol **	Median Survival (wks)
Dow, et al.	7	6 MV linac	40 Gy	4 Gy x 10 fx	106
Mauldin, et al.	10	Cobalt-60	54 Gy	3 Gy x 18 fx	10
Theon, et al.	24	Cobalt-60	48 Gy	4 Gy x 12 fx	46.8 +/- 23.6

\*Radiation sources are external beam megavoltage machines, Cobalt-60 and linear accelerators (linac).

\*\*Radiation protocols are described in terms of dose per fraction (Gy) times the total number of fractions (fx) given.

In one study using 250 kV orthovoltage irradiation, 14 dogs with intracranial masses received either 39 or 45 Gy over 25 to 41 days. These dogs receiving radiation therapy had better survival rates than dogs reported in the literature that received no treatment (mean and median of 345 and 489 days versus 30 and 81 days). Dogs receiving 45 Gy did better than those receiving 39 Gy with a median survival of 519 days and 153 days, respectively [17]. Another study of 4 dogs reported a mean survival time of 322 days in dogs with intracranial tumors receiving 30 to 36 Gy of external beam radiation [14]. A larger, retrospective study of 86 dogs with brain tumors found that dogs that were treated with external beam radiation lived significantly longer than dogs treated with surgery or symptomatic treatment [16]. In this same study, it was found that dogs with mild or moderate initial neurologic dysfunction had a better prognosis than dogs with severe initial neurologic impairment [16]. A recent retrospective study of 29 dogs with intracranial masses treated with radiation therapy alone reported a median survival of 250 days [25]. Cobalt-60 radiation was delivered in 3 Gy fractions on a daily, Monday through Friday basis for a total of 48 Gy in 28/29 dogs and meningioma was the presumptive diagnosis in 22/29 dogs [25]. A less intensive radiotherapy protocol has been advocated by one group [23]. This retrospective analysis of 83 dogs with intracranial masses treated with a hypofractionated radiotherapy protocol reported a median survival of 43.7 weeks. Late radiation toxicity was suspected as the cause of death or euthanasia in 12 dogs by the authors; the radiotherapy protocol was escalating weekly doses of 5, 7, 8, 9, 9 Gy [23]. The large fraction size used to irradiate late responding tissue (brain) would be expected to result in signs of late radiation toxicity.

Radiation therapy is a useful adjuvant therapy to surgery [24,32,52]. Twenty dogs with incompletely resected meningiomas treated with external beam radiotherapy had median progression-free survival rates of  $30 \pm 9$  months [24]. In this same study, immunostaining of the tumors detected progesterone receptors in 14/20 dogs, suggesting a potential role for hormonal therapy in canine meningioma [24]. A more recent study compared surgery alone or surgery followed by radiation therapy for the treatment of intracranial meningiomas [52]. Twenty-six dogs were included in this study; 14 treated with surgery alone and 12 treated with surgery and adjuvant radiotherapy. Median survival times were significantly better for dogs treated with surgery followed by radiation therapy (16.5 months) as compared to surgery alone (7 months) [52].

Canine pituitary tumors respond to external beam radiotherapy [15,21,22]. The space occupying affect of pituitary macrotumors can cause neurologic signs [15,22]. Unlike the human counterpart, canine pituitary tumors are less amenable to surgical excision due to pituitary gland anatomy and tumor extension into the hypothalamus [33]. Radiation therapy is an effective treatment for these tumors to alleviate neurologic symptoms. Radiation therapy has resulted in a reduction in tumor size in both endocrine-inactive and functional pituitary tumors [15,20-22]. Response of functional pituitary macroadenomas and macroadenocarcinomas to radiation alone or radiation and mitotane therapy was evaluated in 6 dogs prospectively with a reported mean and median survival of 740 and 743 days. All dogs had a reduction in tumor size and resolution of neurological deficits [15]. A more recent study of 24 dogs with pituitary macrotumors reported a significant correlation between relative tumor size and severity of neurological signs and between relative tumor size and remission of neurological signs after irradiation [22]. This study reported a median overall survival rate of  $11.7 \pm 5.9$  months, [22] supporting the efficacy of radiotherapy for pituitary macrotumors. However, in a report of 6 dogs with pituitary-dependant hyperadrenocorticism (PDH) (with detectable pituitary tumors but without neurologic abnormalities) treated with external beam radiotherapy, there was inadequate control of clinical signs of PDH in 5/6 dogs [21]. Tumor size decreased in all dogs and was no longer visible in 4 [21]. Dogs with significant neurologic signs and larger tumors have a poorer prognosis [22]. Radiation therapy may be indicated in cases of PDH with macrotumors to reduce or eliminate these masses before neurologic signs become evident. Radiation therapy was also used to treat 3 cats with acromegaly and insulin-resistance diabetes mellitus with a mass in the area of the pituitary gland identified on CT. After completion of radiotherapy, insulin

requirements were decreased in all cats, although transient in one. Diabetes mellitus resolved in 2 cats [20]. A more recent report describes the use of radiotherapy in the treatment of pituitary tumors in 5 cats [53]. In this study diagnosis was based on either CT or MR imaging. A mean total dose of 39 Gy was delivered on a Monday, Wednesday, Friday schedule with median survival times of 15 months, (range 5.5 - 20.5 months) [53]. The 3 cats presenting with neurologic signs showed marked improvement during and/or after the course of radiotherapy and one of two cats with diabetes mellitus and acromegaly had a significant reduction in insulin requirements [53].

**Radiation Therapy for Granulomatous Meningoencephalomyelitis** - Radiotherapy is advocated for treatment of granulomatous meningoencephalomyelitis (GME) in dogs [19]. GME is an idiopathic, inflammatory disease of the CNS in dogs, characterized by large perivascular accumulations of mononuclear cells in the parenchyma and meninges [34]. Radiation is proposed as a treatment for GME on the basis that GME may represent primary B-cell lymphoma [35]. In a retrospective study of 42 dogs with histologic confirmation of GME, a significant increase in survival was seen in dogs that received radiation [19]. Necropsy findings in 3 dogs that received radiation had no evidence of GME in irradiated areas of the brain, suggesting treatment efficacy [19].

### **Radiotherapy of Spinal Cord and Peripheral Nerves**

**Basic Principles and Techniques** - Tumors of the spinal canal can be either intramedullary, intradural-extramedullary or extradural in location. Tumor types include meningioma, neuroepithelioma, ependymoma and nerve sheath tumors; osteosarcoma is the most common extradural tumor (see Spinal cord tumors). Myelography is usually performed when a spinal cord mass is suspected, but CT and MRI scanning provide additional information. In human medicine, MRI has replaced myelography and CT as the imaging study of choice for evaluation of tumors of the spinal canal [36].

Generally, parallel-opposed lateral portals are used to treat spinal cord tumors in companion animals (Fig. 3). Treatment field borders should encompass two vertebral bodies above and below the tumor as defined by myelography to avoid marginal miss. Treatment plans can be one-dimensional (manual calculation of dose at a weighting point) or computer based. Portal localization radiographs should be taken at initiation of treatment to verify radiation treatment field.



Figure 3. Photograph of a radiation treatment set-up using Cobalt-60 in a dog with an incompletely resected nerve sheath tumor located at the level of the cranial lumbar vertebrae. The patient is treated with parallel opposed lateral fields with the dose centered at mid-body. Skin markings are made to facilitate daily treatment set-up. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

**Vertebral and Spinal Cord Tumors** - Radiation therapy has been used postoperatively in the treatment of spinal cord tumors in human and veterinary medicine [26,36,37]. The same radiobiological considerations and treatment protocols discussed earlier in the brain section hold true for the spinal cord. Radiotherapy of spinal cord tumors is indicated in the post-operative setting after decompression laminectomy of the primary lesion. In a study of dogs treated either with radiotherapy and chemotherapy (n = 6) or surgery, radiotherapy and chemotherapy (n = 8) for primary and metastatic osteosarcoma and primary fibrosarcoma vertebral tumors in dogs the median survival time was 150 days [37]. This was not significantly different than median survival times for dogs treated with surgery or surgery and chemotherapy (n = 6) [37]. A study of 9 dogs with spinal cord tumors irradiated after decompressive surgery reported a median survival time of 17 months [26]. The majority of tumors in this study were meningiomas [26]. In a study of 22 dogs with spinal tumor treated with surgery alone, the median survival time was 240 days [38]. Although it is a relatively small study, it appears that adding radiotherapy to surgery for spinal cord tumors increases survival as compared to surgery alone [26].

**Malignant Peripheral Nerve Sheath Tumors** - Malignant peripheral nerve sheath tumors (MPNST) (see Peripheral nerve tumors) are amenable to postoperative radiotherapy. Computer based treatment planning is preferred using CT examinations obtained post surgery. Six dogs treated at the University of Wisconsin, School of Veterinary Medicine with MPNST in the post-operative setting had a median survival time of 448 days.

**Lymphoma** - In terms of radiosensitivity, lymphoma responds rapidly to lower doses of radiation as compared to other tumors. This is because lymphocytes die an intermitotic, early death due to apoptosis. Apoptosis is programmed cell death, which is characterized by a stereotyped sequence of morphologic events [39]. Radiation-induced cell death via apoptosis is highly cell-type dependent in which hemopoietic and lymphoid cells are prone to rapid cell death by the apoptotic pathway [39]. Unfortunately, lymphoma is often a multisystemic disease and rarely localized [40], therefore radiotherapy is not an



optimal treatment modality. Whole body irradiation is fraught with normal tissue complications, both acute and late effects [41]. Localized radiotherapy for dogs and cats with spinal lymphoma in the postoperative setting can provide clinical improvement, but does not address the systemic nature of the disease or the propensity for positive titer for feline leukemia virus in cats [40,42,43]. Craniospinal radiotherapy where the entire neuroaxis (brain and spinal cord) is irradiated has been reported in combination with chemotherapy in the treatment of CNS lymphoma in dogs [42]. In this study a marked response was reported in 4 dogs treated with a combination of systemic chemotherapy, intrathecal chemotherapy and craniospinal irradiation, however, the effect was not durable [42].

### **Chemotherapy**

Chemotherapy has been reported sporadically in combination treatment with radiotherapy of CNS tumors [16,42]. In human medicine chemotherapy is used as an adjuvant to irradiation or surgery for intracranial tumors [13]. The blood-brain barrier limits delivery of chemotherapeutic drugs. Drugs with lipid solubility such as nitrosoureas, vincristine, cisplatin and procarbazine may reach therapeutic levels with the CNS [13]. Intrathecal injection of chemotherapeutic agents into the CSF space has been used, but only a limited number of agents are suitable. These include thiotepa, methotrexate, and cytosine arabinoside [13].

Chemotherapy has been used in combination in a small number of dogs with spinal cord tumors [37,38]. In these studies the addition of chemotherapy had no significant impact on overall survival.

### **Sequelae of Treatment**

Acute Toxicity of the Brain - Although relatively uncommon, acute toxicity secondary to radiation therapy of the CNS can occur. This is manifested by a transient worsening of clinical signs occurring early in the treatment course and is a result of peritumoral edema [13]. Patients usually respond to a short course of corticosteroids. Persistent or refractory clinical signs may indicate tumor progression. Otitis externa can occur if the ears are in the treatment field. This is less severe with daily instillation of ear medication containing corticosteroids, which is started at the onset of treatment. Acute radiation reactions are generally well tolerated and self-limiting. These include epilation, otitis, and when the eyes are included in the treatment field, conjunctivitis, keratoconjunctivitis and corneal ulcers. Acute radiation side effects will subside within 3 - 5 weeks after completion of therapy. Neurologic deterioration may occur as an "early-delayed" or subacute side effect in the 6 to 12 week period after completion of therapy. This subacute toxicity is attributed to capillary permeability changes and transient demyelination secondary to damaged oligodendroglial cells [13]. Patients will usually respond to a course of corticosteroid therapy, improving over several months. However, it is difficult to differentiate subacute toxicity from tumor recurrence.

Late Toxicity of the Brain - Late sequelae to irradiation of brain tissue may appear 6 months to many years after completion of therapy, with the most serious being radiation necrosis [13]. Radiation necrosis can be difficult to differentiate from recurrent tumor. In both entities the patient will have progressive reappearance of clinical signs, an enhancing mass on computed tomographic (CT) images, and surrounding brain edema. Chronic radiation reactions can include permanent skin epilation and pigment change, atrophy of temporal muscle, keratitis with corneal vascularization, cataracts, and deafness. In one study, where brain tissue in the radiation target volume was examined at necropsy in 10 dogs treated with radiotherapy for pituitary macrotumors, demyelination and reactive parenchymal gliosis was observed in dogs where large treatment fields relative to head size were used [22]. Radiation protocol in this study was 4 Gy fractions for 12 treatments [22] and supports the use of smaller fraction sizes when irradiating the CNS. To reduce the probability of late effects to less than 5%, the total dose should be limited to 48 Gy or less in 3 Gy or less fractions [44].

Radiation Toxicity of the Spinal Cord - A transient, reversible myelopathy can occur within 2 - 6 months after completion of radiation treatment of the spinal cord and changes are thought to be related to transient demyelination of the treated length of spinal cord [36]. Chronic progressive or delayed myelopathy can occur months to years after treatment. Permanent myelopathy presents as progressive neurologic signs, including paresthesias, motor weakness, and loss of pain or temperature sensation [36]. The occurrence of this irreversible myelopathy is dependent on total dose, fraction size, and volume of cord treated. In the dog, 44 Gy given in 4 Gy fractions to a 20 cm length of spinal cord has less than a 1% probability for radiation myelopathy [45,46]. In a study evaluating peripheral nerve tolerance of single large radiation doses, the 5% probability of injury (ED<sub>5</sub>) for canine peripheral neuropathy was approximately 15 Gy [47]. In that same study, 80 Gy given in 2.67 Gy fractions caused little clinical evidence of nerve injury [47]. This study shows the effect of dose per fraction in irradiation of late responding tissues of the CNS. Radiation injury to peripheral nerve appears to be the result of direct radiation effects on Schwann cells and nerve vasculature and secondary effects resulting from damage to regional muscle and vasculature [48].

Radiation Neuropathy - Radiation neuropathy can occur secondary to the treatment of any tumor when peripheral nerves are in the radiation field. Lameness and muscle atrophy can occur. Documentation of radiation neuropathy in the veterinary

literature has only been reported with single doses of greater than 15 Gy such as given for intraoperative radiotherapy (IORT) [47,49]. There are sporadic case reports of peripheral neuropathy in the human literature [50,51].

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## Evaluation and Management of Behavioral Conditions (19-Nov-2001)

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### Introduction

Psychiatric disorders - whether in humans or in domestic animals where they are called behavioral disorders - are among the most complex and incapacitating of all pathological conditions. In the USA 20 million patients suffer from depression, manic depression, and schizophrenia. The direct and indirect cost for the treatment of schizophrenia, alone, is \$33 billion per year, similar to the combined costs of the treatment of arthritis and coronary artery disease [1].

The data from the literature on canine and feline behavioral disorders are equally impressive. Behavioral disorders are responsible for the relinquishment and death of more pet animals per year than infectious, neoplastic, and metabolic disease, combined. In the early 1990s, the average veterinary practice in the USA was estimated to lose in excess of \$17,500 in income annually for services that were not delivered because the pets were relinquished due to behavioral concerns [2]. More recent estimates of behavioral problems suggest that this may be a gross under-estimate [3,4].

Until the 1990s became the decade of the brain and neuroscience in the USA, the tendency was to neatly cluster "neurological" conditions as separate from those considered "behavioral". Neurological conditions tended to be considered as those with discrete somatic pathologies, whereas behavioral conditions, by definition, were viewed as nebulous phenomenon that were the result of an often stated but poorly understood interaction between the physical and genetic environments. Such an absolute and simplistic view had as logical sequelae the views that:

1. all dogs and cats were inherently normal, but their behaviors could be inappropriate or undesirable,
2. if the dog or cat exhibited inappropriate or undesirable behaviors, such behaviors were the result of inadequate guidance from the owner, and
3. appropriate training could fix all concerns about dog behaviors, whereas cats were best left to their own devices as outdoor cats where they could revert to their "normal" state.

Without exception, none of these views is true, and they are - mostly - not often uttered now, although there is still substantial support for the stated views regarding cats. Veterinarians who are general practitioners are committed to providing total patient care. They should be in the position to evaluate deviations from normal behavior and to suggest solutions before the problem worsens. The activities of trainers and handlers are predicated on normal behavior and on the assumption that all problems are management related. While management may play a role in both the expression of behavioral problems and their resolutions, it would be inexcusable and irresponsible to advance poor management as the primary etiology of behavioral disorders. The vast majority of animals with behavioral problems are not poorly managed or misbehaved; they are abnormal or are responding to an abnormal social system [5]. In this context these problems are "organic" in nature - the "organic cause" is a dynamic one, and now encompasses disorders of neurochemical metabolism that underlie many, if not most, behavior problems.

The decade of the brain and of neuroscience forced us to confront the fact that we and our patients are functionally bags of interacting genes and chemicals, and that the nature versus nurture question may be sufficiently simplistic to no longer be heuristically useful.

In light of the findings of regional brain activity and neurotransmitter interaction and dysregulation, it may be a more useful paradigm to consider neurology and behavioral medicine as different points on the same continuum/response surface, or as functions of the scale at which the diagnosis is made and treatment addressed. This position is supported by data from both humans and animals indicating that behavioral changes are the function of, or result in altered regulation of neurochemical function, or dysregulation of neurochemical function. Given this, the pathologies in behavioral medicine are just as organic, although possibly harder to evaluate, as those involved in brain tumors.

## **Diagnosis in Behavioral Medicine**

- The Importance of Terminology
- The Importance of Mechanism of Level of Resolution

## **Definitions of Common Conditions**

### **The Conundrum Posed by the Neurological/Behavioral Continuum**

- Canine Dominance Aggression
- Canine Obsessive-compulsive Disorder
- Canine Cognitive Dysfunction

## **Neurobehavioral Genetics, Neuroanatomy, and Fears and Anxieties**

## **Anxiety and Related Psychopharmacology**

## **Neurotransmitters and Neurochemical Tracts**

## **Classes of Drugs Used And Misused in Behavioral Medicine**

## **Mechanism of Action of Serotonergic Agents**

## **Pre-medication Considerations**

## **Monitoring**

## **Withdrawal from Medication**

## **Conclusions**

## **Appendix of Drugs Dosages**

### **Diagnosis in Behavioral Medicine - The Importance of Terminology**

Behavioral medicine, unlike other specialties in veterinary medicine, does not have a protected vocabulary. Words that are in common daily usage are often used within the framework of the diagnosis. This has advantages in that the clients are speaking the same language as the veterinarian. The disadvantage is that without a protected vocabulary there is no guarantee that the same definition or context is agreed upon for any of the terms used. Accordingly, it is essential that anyone engaging at any level in the practice of behavioral medicine be very careful about the words they use and their perceived meanings. Associated difficulties can be avoided by defining all terms that are used. The intent here is to ensure that, regardless of anyone's personal definition, the criteria for contextual discussion of the problem at hand are clear.

Also, if the words you choose as labels affect your interpretation and thinking about processes for which you have incomplete information, the actual words become very important. Nowhere is this more important than in behavioral medicine - a field for which signs have (usually erroneously) been viewed as "soft", and for which few simple tools that permit reasonably unambiguous comparison (e.g., a gas chromatograph or refractometer) are available. In fact, only after one is assured that all workers in the field are using the same diagnostic criteria, can any comparisons be made at the population level. The fraction of animals afflicted by a specific behavioral problem is real, but the labels we place on those animals may not be consistent across populations, so that demographic data may not, in fact, reflect the underlying frequency or occurrence of the problem. If this is true, comparisons of efficacy of treatment across populations may be suspect. Cultural patterns of human impact of the behavioral problems of pets can only be assayed using multicenter studies. When well done, such studies can detect underlying sources of variation that suggest causal mechanisms for disorders that may not have been previously appreciated, but such comparisons are invalid if the same rules were not used to formulate the diagnoses (e.g., the "data" here) [5].

In humans, a label like "depression" may refer to a symptom, a syndrome, or a nosological entity [6-9]. Because we assess what we have come to define as depression in humans largely by a series of verbal responses, we use data that are, at best, correlates of underlying pathology. Observable changes in behavior that occur in rodents, which serve as models for human depression, are treated as secondary symptoms in humans, and little effort is made to characterize either human or rodent behaviors in a manner that would allow assessment of analogy or homology. These concerns are central to diagnostic conundrum in both human psychiatry and veterinary behavioral medicine, and have implications for understanding the underlying mechanism of the pathology and for treatment [5,9-12].

### **The Case for the Use of Necessary and Sufficient Conditions**

Implicit in all diagnostic categories, unless explicitly stated, is that there is no known underlying gross physical or physiological reason for the behavioral problem, and that gross physical and physiological "causes" have been ruled out. It is also important to remember that as they are listed here these classifications represent diagnoses of problem behaviors, not just descriptions of a behavioral event (i.e., dominance aggression can **only** be a diagnosis for an abnormal behavior, but interdog aggression can be both a diagnosis and description).

The implementation of "necessary and sufficient" criteria, using the terms as they are used in logical and mathematical applications, is a refinement over descriptive definitions of terms. The imposition of necessary and sufficient diagnostic criteria act as qualitative, and potentially quantitative, exclusion criteria. They allow for uniform and unambiguous

assessment of aberrant, abnormal, and undesirable behaviors [13].

A **necessary** criterion or condition is one that must be present for the listed diagnosis to be made. A **sufficient** criteria or condition is one that will stand alone to singularly identify the condition. Sufficiency is an outcome of knowledge: the more we learn about the genetics, molecular response, neurochemistry, and neuroanatomy of any condition and its behavioral correlates the more succinctly and accurately we will be able to define a sufficient condition. Definition of necessary and sufficient conditions is not synonymous with a compendium of signs associated with the condition. The number of signs present and the intensity of those may be a gauge for the severity of the condition, or act as a flag when there can be variable, non-overlapping presentations of the same condition [5]. This approach is similar to that taken by the American Psychiatric Association for the Diagnostic and Statistical Manual (most recent edition = DSM-IV). The conditions that are of interest in veterinary behavioral medicine do not have to be exact analogues of human conditions for this type of classification to be meritorious. In veterinary behavioral medicine we do not yet have the data on large numbers of patients from varied centers that allow human psychiatrists to use clusters of signs to help with diagnosis; however, the criteria for human psychiatric disorders are not based on non-specific signs, either. They are based on definitional criteria that are descriptive, and the non-specific signs are nested within the stipulation made by those criteria [14].

The approach endorsed here provides for a mechanism to collect behavioral data from a variety of populations across time, and to compare those data. Comparisons of data predicated on this classification scheme should engender revisions and refinements of the classification. The classification, itself, is not important: the extent to which it provides a structured, logical, heuristic tool for the development of thought in the field **is** important [13].

Any joint theoretical/clinical approach to studying abnormal behavior should include the following goals:

- a description of the specific behavioral profiles and response surfaces (multi-dimensional) of those profiles;
- postulated levels of mechanism in which to examine potential profiles and response surfaces;
- tests of these postulates by a) breeding for the behavior, b) cataloging response to treatments in controlled and double blind fashions, and imaging of patients (CT, MRI, functional MRI, PET and SPECT scans).

### **Diagnosis in Behavioral Medicine - The Importance of Mechanism of Level of Resolution**

When one makes a behavioral diagnosis one is usually making the diagnosis on the basis of some descriptor of the behavior. Such diagnoses are functional, phenotypic, or phenomenological diagnoses. They are based on the patterns of the behaviors or on profiles of behavioral sequences. Diagnosis at this level may hint at underlying neuroanatomical, neurochemical, molecular, or genetic forces or mechanisms driving the abnormality, but phenotypic diagnoses are not pathognomonic for any of these further discrete, mechanistic levels.

The most common error made in diagnostic approaches that rely on description is to confuse or confound levels of mechanism within descriptions of diagnosis. It is important to realize that tests for mechanistic hypotheses must occur within the level for which the mechanism is specified. For example, tests of a putative neurochemical basis for a behavioral problem must be tested at that level, not only at the more gross level of changes in behavior, although the result of the test may be changed behavior. This approach is outlined in Table 1.

Part of the problem in identifying the relative contributions of the different mechanistic levels to overall behavioral presentation is that most of the data available (e.g., behaviors associated with specific environmental stimuli; alterations in behavior in response to drug therapy) are only correlations. Correlational data can suggest tests of potential hypotheses of causality, but such data are not synonymous with "cause" or mechanism, itself. Diagnoses are not diseases; correlation is not causality. The assumption that they are equivalent is epistemologically insufficient. This assumption is the most common error made in thought about most processes, including normal and abnormal behavior.

Conditions for which there is putative etiologic and pathophysiologic heterogeneity (multi-factorial disorders) are complex. Diagnosis and treatment will be complex. For example, not all tail-chasing is due to the same underlying neurophysiological mechanism (See Table 1), but unless there are criteria for diagnosis and description, and a heuristic framework within which to separate various causal or mechanistic aspects of diagnosis, we will not be able to distinguish between different causes of tail chasing.

Phenotypic (functional, phenomenological) diagnoses are open to various mechanistic bases at all lower levels. Some of these more reductionistic levels can be partially tested using treatment (specific pharmacologic agents), but few phenotypic diagnoses can be specifically tested using behavior modification. Regardless, the logic for using very specific phenomenological diagnoses is to (a) enumerate and identify the particular behavioral manifestation that needs to be altered or assessed, and (b) to identify areas where specific behavioral intervention can be useful.

**Table 1. Understanding Patterns of Behavior within Levels of a Mechanistic Approach**

**I. Phenomenological, phenotypic, functional diagnoses: must meet necessary and sufficient terminological criteria**

**A. Demographic patterns**

1. Global patterns of behavioral change with age and neutering (must follow individuals through time)

**B. Suites of behavioral patterns**

1. Specific behaviors that occur
  - a. Number of behaviors that occur (range, mean, predictive value)
  - b. Covariation in behaviors to define subtypes or subpopulations (Venn diagrams, r values) - must avoid spurious correlations
  - c. Ontogenetic development of specific behavioral suites (ethograms) (must follow individuals)
2. Elemental behaviors that are shared across diagnoses (may hint at underlying reductionist mechanism - i.e., the neurochemistry of stress)

**II. Neuroanatomical diagnoses**

**A. Region activated during normal versus abnormal behavior**

1. Level of activity
2. Variants in patterns of activity

**B. Neuron behavior**

1. Types
2. Densities
3. Overall activity

**III. Neurochemical/Neurophysiological diagnoses**

**A. Types of neurochemicals**

1. Activities
2. Receptor types associated with these
  - a. Activity of receptor gates
  - b. "Metabolism" of receptors
  - c. Conformation of receptors

**B. Interactions of neurochemicals**

1. Neuron recruitment
  - a. Regional activity
  - b. Responses to behavioral changes

**IV. Molecular diagnoses**

**A. Molecular/conformational chemistry of receptors and neurotransmission**

**B. Gene product regulators of expression**

**C. Gene product regulators of function**

**V. Genetic diagnoses**

**A. At the level of gene/locus**

1. Overall heritability (Mendelian pattern)
  - a. Codon shifts
  - b. Errors (loss or addition of part of chromosome - e.g., Marshall's disease, Down Syndrome)
  - c. Coding for different proteins
2. Multi-factorial effects

**B. At the level of genome**

1. Gene products
2. Regulator genes
3. Local environmental receptor effects

**Note:** tests of mechanistic hypotheses must occur at the level of focus.

Inherent in the nature of a functional or phenotypic diagnosis is the association of a compilation of what are relatively non-specific signs. Growling is no more specific a sign than is an elevation in temperature, yet the distinction between compilations of signs and diagnosis has often been blurred in behavioral medicine. Some of the difficulty is the result of the fact that behavior is so complex. Behavior can be both an event and a process, and observable behaviors are the result of the integration of all of the processes ongoing in underlying organ systems, in interaction with the external social and physical environments. The integration of processes inadvertently encourages tautological diagnoses. Careful thought is necessary to avoid tautology. One mechanism whereby tautology can be avoided is to specify necessary and specific conditions for diagnosis, separately from compendia of non-specific signs. Once these conditions are specified, lists of signs and frequencies with which those signs occur can be compiled for each diagnosis, allowing within and between level population comparisons. Differences could reflect cultural or environmental effects on the manifestation of frequencies of constellations of signs, and would allow comparisons of intensity or relatedness of individual diagnoses when they occur singly compared to when they occur in tandem with other diagnoses. Knowledge of the frequency of specific behaviors is useful for:

1. establishing an overall pattern of the behavior [a. suites of behavioral patterns, b. determining heterogeneity of condition (how variable is it?), c. mechanistic tests of causality];
2. intervention;
3. danger assessment, and
4. prognosis. These components are not synonymous with a diagnosis.

Finally, it is essential to understand that the model presented in Table 1 is **not** merely a behavioral recapitulation of the standard paradigm of diagnostic pursuit (e.g., first a clinical diagnosis is made, then a laboratory or radiographic diagnosis is made, then a pathological diagnosis, etc.). In behavioral medicine the "levels" of diagnoses interact in a dynamic and complex manner. How an animal behaves affects which areas of the brain are active and the degree to which they are active, which, in turn, affects regional neurochemistry. The behavior can also affect the neurochemistry directly, and both the behavior and the neurochemistry can have an effect on the molecular effects on receptor configuration. Rather than view these as nested diagnostic levels, each of these levels should be viewed as dynamic, variable, interactive response surfaces. In this model the genomic response surface sets boundary conditions that define the extent to which the other responses surfaces can respond in a fluid manner and can be plastic in their interactions with other levels of response surfaces. The approach discussed tracks the number and type of diagnoses, number and type of signs, and population level and temporal differences, without confounding these as occurs when diagnosis is indistinguishable from lists of signs. This approach generates data that could then provide hypotheses for which tests could be directed at each individual level. For example, if two diagnoses were phenotypically different, but neurochemically indistinct, this suggests that the differences in the phenotypic presentation are due to environmental, social, or cultural effects. If, on the other hand, one diagnosis is shown to have two neurochemical bases, the resultant behavior can be due to underlying differences in physiology and genetics plus any overlying effects of the environment (See Table 2A & Table 2B for examples).

Table 2A. Example for Consideration of Interaction of Phenotypic Level of Mechanism with others				
Phenotype	Abnormal Variant A	Abnormal Variant B	Abnormal Variant C	"Normal" D
Neuroanatomical Variant	I	I	I	I
Neurochemistry	a	b	a	b
Molecular Products	I'	II'	II'	II'
Genotype	a'	b'	b'	b'

In this example the variants in the condition are due to some difference in environmental response. This could be a purely phenotypic effect (Abnormal variant B). Alternatively, the effect could be due to learning and long-term potentiation (in which case the molecular level is affected - Abnormal variant A); this molecular effect also affects neurochemistry. The effect could also be one of neurochemistry, without affecting the molecular level (Abnormal variant C).

Table 2B. Example for Consideration of Interaction of Phenotypic Level of Mechanism with Others			
Phenotype	Abnormal Variant A	Abnormal Variant B	"Normal" C
Neuroanatomical Variant	I	I	I
Neurochemistry	a**	b	b
Molecular Products	I'***	II'	II'
Genotype	a'	b'	b'



In this example the variants in the condition are due to some difference in environmental response. This could be a purely phenotypic effect, as presented. Alternatively, the effect could be due to learning and long-term potentiation (in which case the molecular level is affected) or the effect could be one of neurochemistry. The two latter choices are reflected as (\*\*).

Fears, phobias, anxieties, and obsessive-compulsive disorders (OCDs) are among the most difficult behavioral problems to diagnose and treat. There is probably no other area in behavioral medicine that is fraught with such confusion and opinion. Historically, many anxiety-related conditions, including those involving impulsive aggression, have been viewed as neurological conditions involving seizure activity. This assumption has led to treatment with barbiturates, as for a seizure disorder, which has often initially mitigated the clinical signs experienced by the patient. It would be a mistake to think that response treatment with any medication commonly used to control any kind of epilepsy or seizure activity confirmed the presence of such activity. Rather, it is necessary to understand the gross neurochemical pathways involved in these conditions, their locations and interactions, and how they are affected by medications used to treat them.

Fear and anxiety are probably closely related, but may not be identical at the neurophysiological level. It is worth remembering that when one diagnoses a problem related to fear or anxiety one is doing so at the level of the phenotypic or functional diagnosis, but such conditions are treated at this level and, when psychotropic medication is used, at the neurophysiological level.

### Definitions of Common Conditions that may be Concerns for those Evaluating Neurological Diagnoses

As already discussed, diagnosis may not be as simple or clear-cut as a definition. Given that we do not understand the manner in which the "causal" levels interact to produce the problem, we can only evaluate the form that interactions take phenotypically. Clear use of terminology can help to make apparent the parts that are consistent and that we can understand and separate them from those that are more complex. While these definitions are clear, the conditions for which they are relevant may be multi-factorial and heterogenous. Table 3 contains the preferred and accepted definitions of general behavioral descriptors that are used in both neurology and behavioral medicine, as well as psychiatry. Table 4 contains the necessary and sufficient diagnostic criteria for behavioral diagnoses that may frequently be considered as differential diagnoses for the putative neurological patient. One can see by the definitions of epilepsy and seizure that these terms could be used to describe virtually all behavioral conditions, without actually providing any information about them. Again, such inexactitude is an historical artifact related to how we began to understand neurological and behavioral conditions that has virtually no relevance for modern approaches to behavior. In part, the diagnostic scheme discussed and demonstrated in Table 4 was created in response to an informational vacuum with respect to phenotypic behavioral characterization.

**Table 3. Preferred and Accepted Definitions of often Discussed General Behavioral Conditions**

**Abnormal behavior:**

Activities which show dysfunction in action and behavior.

**Anxiety:**

Anxiety is the apprehensive anticipation of future danger or misfortune accompanied by a feeling of dysphoria (in humans) and, or somatic symptoms of tension (vigilance and scanning, autonomic hyperactivity, increased motor activity and tension). The focus of the anxiety can be internal or external.

**Convulsion:**

Seizure with generalized motor impairment.

**Displacement activity:**

An activity which is performed out-of-context, or "displaced", because the animal is "frustrated" in its attempt to execute another activity or otherwise occupy itself. This is considerably less specific than redirected activity which implies a substitution of behavior "in kind", but towards another target. In cases where displacement activity is involved the activity may not be "in kind".

**Epilepsy:**

A disorder of the brain that is characterized by recurring seizures.

**Fear:**

A feeling of apprehension associated with the presence or proximity of an object, individual, social situation, or class of the above. Fear is part of normal behavior and can be an adaptive response. The determination of whether the fear or fearful response is abnormal or inappropriate must be determined by context. For example, fire is a useful tool, but fear of being consumed by it, if the house is on fire, is an adaptive response. If the house is not on fire, such fear would be irrational, and, if it was constant or recurrent, probably maladaptive. Normal and abnormal fears are usually manifest as graded responses, with the intensity of the response proportional to the proximity (or the perception of the proximity) of the stimulus. A sudden, all-or-nothing, profound, abnormal response that results in extremely fearful behaviors (catatonia, panic) is usually called a phobia.

**Table 3. Preferred and Accepted Definitions of often Discussed General Behavioral Conditions**

**Mental disorder (not generally used in veterinary behavioral medicine):**

Clinically significant behavior of psychological syndrome or pattern that occurs in an individual and that is associated with present distress (e.g., a painful symptom) or disability (i.e., impairment in one or more areas of functioning) or with a significantly increased risk of suffering death, pain, disability, or a loss of freedom." [14]. Regardless of cause, the disorder is a "manifestation of a behavioral, psychological, or biological dysfunction in the individual." [14].

**Obsessive-compulsive disorder:**

An APA classification of abnormal behaviors that have as characteristics recurrent, frequent thoughts or actions that are out-of-context to the situations in which they occur. These behaviors can involve cognitive or physical rituals, and are deemed excessive (given the context) in duration, frequency, and intensity of the behavior. One of the hallmarks of this condition that distinguishes it from motor tics, etc., is that OCD behaviors follow a set of rules created by the patient. The condition in domestic animals is probably similar and analogous through descent, and probably includes stereotypies, self-directed behaviors, etc. Regardless, the behavior must be sufficiently pronounced to interfere with normal functioning.

**Phobia:**

A sudden, all-or-nothing, profound, abnormal response that results in extremely fearful behaviors (catatonia, panic) is usually called a phobia. An immediate, excessive anxiety response is characteristic of phobias. Phobias usually appear to develop quickly, with little change in their presentation between bouts; fears may develop more gradually, and within a bout of fearful behavior, there may be more variation in response than would be seen in a phobic event. It has been postulated that once a phobic event has been experienced, any event associated with it or the memory of it is sufficient to generate the response. Phobic situations are either avoided at all costs, or if unavoidable, are endured with intense anxiety or distress.

**Redirected activity:**

Direction of an activity away from the principal target and toward another, less appropriate target. This is usually best identified when the recognized activity is interrupted by the less appropriate target or by a third party, and, in contrast to displacement activity, redirected activity appears to be a substitution "in kind" of the interrupted behavior.

**Separation anxiety:**

When animals exhibit symptoms of anxiety or excessive distress when they are left alone the condition is called separation anxiety; however, the most commonly exhibited behaviors (elimination, destruction, excessive vocalization) are only the most visible signs of anxiety. Drooling, panting, and cognitive signs of anxiety will not be diagnosed but probably occur.

**Seizure:**

Synonymously used with fits and convulsions, a term used to describe the manifestations of abnormal brain function that are characterized by paroxysmal stereotyped alterations in behavior.

**Stereotypy:**

A repetitious, relatively unvaried sequence of movements which have no obvious purpose or function, but that are usually derived from contextually normal maintenance behaviors (e.g., grooming, eating, walking). Inherent in the classification of dysfunction is that the behavior interferes with normal behavioral functioning.

**Vacuum activity:**

An activity involving an instinctive, unconscious, or response behavior in the absence of the stimulus that would elicit that behavior. Such activity seemingly has no apparent, contextual, useful purpose.

**Table 4. Necessary and Sufficient Conditions for Selected Behavioral Diagnoses Associated with Anxiety in Small Animals, and with Relevance to Patients for whom Neurological Diagnoses may be a Concern (adapted from [15].)**

**Behavioral Diagnosis: Cognitive dysfunction**

**Necessary and Sufficient Conditions:** Change in interactive, elimination, or navigational behaviors, attendant with aging, that are explicitly not due to primary failure of any organ system.

**Behavioral Diagnosis: Dominance aggression (perhaps better labeled canine impulse control aggression)**

**Necessary Condition:** Abnormal, inappropriate, out-of-context aggression (threat, challenge, or attack) consistently exhibited by dogs towards people under any circumstance involving passive or active control of the dog's behavior or the dog's access to the behavior.

**Sufficient Condition:** Intensification of any aggressive response from the dog upon any passive or active correction or interruption of the dog's behavior or the dog's access to the behavior.

**Table 4. Necessary and Sufficient Conditions for Selected Behavioral Diagnoses Associated with Anxiety in Small Animals, and with Relevance to Patients for whom Neurological Diagnoses may be a Concern (adapted from [15].)**

**Behavioral Diagnosis: Noise phobia**

**Necessary and Sufficient Conditions:** Sudden and profound, non-graded, extreme response to noise, manifest as intense, active avoidance, escape, or anxiety behaviors associated with the activities of the sympathetic branch of the autonomic nervous system; behaviors can include catatonia or mania concomitant with decreased sensitivity to pain or social stimuli; repeated exposure results in an invariant pattern of response.

**Behavioral Diagnosis: Obsessive-compulsive disorder**

**Necessary Condition:** Repetitive, stereotypic motor, locomotory, grooming, ingestive, or hallucinogenic behaviors that occur out-of-context to their "normal" occurrence, or in a frequency or duration that is in excess of that required to accomplish the ostensible goal.

**Sufficient Condition:** As above, in a manner that interferes with the animal's ability to otherwise function in his or her social environment.

**Behavioral Diagnosis: Panic disorder**

**Necessary condition:** sufficient, profound, non-graded, extreme response exhibited out-of-context to the provocative environment, manifest as active avoidance, escape, or anxiety associated with the activities of the sympathetic branch of the autonomic nervous system.

**Sufficient condition:** as above but includes mania or catatonia concomitant with decreased sensitivity to pain or social stimuli; once established repeated exposure results in an invariant pattern of response.

**Behavioral Diagnosis: Separation anxiety**

**Necessary Conditions:** Physical or behavioral signs of distress exhibited by the animal only in the absence of, or lack of access to the client.

**Sufficient Conditions:** Consistent, intensive destruction, elimination, vocalization, or salivation exhibited only in the virtual or actual absence of the client; behaviors are most severe close to the separation, and many anxiety-related behaviors (autonomic hyperactivity, increased motor activity, and increased vigilance and scanning) may become apparent as the client exhibits behaviors associated with leaving.

### The Conundrum Posed by the Neurological/Behavioral Continuum

Most of the ways in which clients recognize that something is wrong with their pets or that their pets are ill involves behavior. Clients may not be able to define "normal" behavior for their pet under non-provocative circumstances, but they are excellent at recognizing when their pet deviates from this. Accordingly, a limp which is the result of a purely somatic condition is first understood and recognized by the client because the dog ceases to run and walks oddly.

The standard DAMNIT scheme for grouping of conditions actually originates in perceived behavioral changes, and then seeks underlying somatic "causes" for the dysfunction. Unfortunately, this heuristic model is inadequate to deal with behavioral conditions that may reflect altered or dysregulated neurochemistry in the absence of any organic or somatic dysfunction. Even the "anomalous" grouping refers primarily to structural developmental defects. The heuristic failure of this classification scheme in behavioral medicine is demonstrated by how often algorithms designed to identify neurological pathology lead to "behavior" or "non-neurogenic X" as a path of last resort [16].

Furthermore, if we wish to explore more refined mechanisms of the behavioral conditions we would have to redefine the accepted terminology in the DAMNIT mnemonic to reflex complex interactions at the cell, molecular, and genomic levels. This is unlikely to happen, and would not necessarily increase our understanding even if it were done.

In part, the difficulty with behavioral medicine is due to the fact that the diagnostic paradigms used in veterinary (and human) medicine have changed little in the last 100+ years, and are inadequate to describe or discuss conditions that are the result of genomic, molecular, or neurochemical dysfunction in the absence of structural or mechanical defects that can be directly measured. To understand behavioral conditions at a level more sophisticated than that of general and broad gene x environment interactions, a paradigm shift is required. In addition to the structured thought process previously discussed, a new paradigm should require that we are careful with our terminology and define the conditions by which phenotypic diagnoses can be made, and that we understand that the behaviors we see are, at some level, the results in complex interactions between DNA, RNA, 2nd messenger systems, trophic factors, receptors, neurochemicals, and tracts and pathways that help define the possibilities for neurochemical interaction. The rest of this chapter will focus on these complex interactions as they are presently understood.

Nowhere is the resultant compromise of our understanding about the behavioral condition more clear than for various behavioral conditions that are termed "seizure disorders". The most common of the behavioral conditions that are often

classified as "seizure disorders" are obsessive-compulsive disorder (OCD), panic disorder, and dominance aggression or canine impulse and control disorder. A short discussion of dominance aggression, OCD, and cognitive dysfunction will indicate the problems faced.

### **Considerations for the Neurobiology of Canine Dominance Aggression**

When considering the application of the necessary and sufficient conditions listed in Table 4 for dominance aggression, it is critical to consider the entire context of the interaction in which the behavior occurs. The classic afflicted dog growls, lunges, snaps or bites if they are stared at, physically manipulated - often when reaching over their head to put on a leash, physically disrupted or moved from a resting site - no matter how gently this is done, and when they are physically or verbally corrected. Otherwise, owners report that these are perfectly wonderful and charming dogs for well over 95% of the time. Owners are further puzzled by the observation that the dog often seeks them out for attention and then bites them when they give it. As for most other behavioral conditions, this one develops or becomes enhanced during social maturity, further confusing owners because the dog was "perfect" for the first 1 - 1.5 years of life. Unfortunately, the age at which the condition most frequently becomes apparent is also the age at which most dogs develop idiopathic epilepsy, further confounding the problem. Most dogs exhibiting dominance aggression/impulse - control disorder are male, although there is a female group that exhibits the behavior beginning in puppyhood, leading to questions of *in utero* androgenization of the brain [17]. Unlike for fear aggression, where the animal intensifies his or her response when escape becomes impossible, dogs with a control disorder take a proactive role in precipitating the events. They do so because of underlying anxiety about contextually appropriate responses in situations involving humans. These dogs are unable to take a more passive role and to obtain, from context, what would be considered acceptable behavior. There are 2 broad classes of this condition: the impulsive or explosive form, and the more common, consistent form where the dog's response and behavior are variable depending on the circumstances and the behavior of the humans involved.

In type 1 of this canine impulse control disorder, the dog appears to fire quickly and without warning, leading many authors to describe "rage" like behaviors [16] or to consider this to be a form of temporal or frontal lobe epilepsy [18]. Again, based on the definition of epilepsy, little information is gained by such a label and much might be lost because we think that we know something when, in fact, we do not. Rage is undefined for domestic animals, and also implies some human value judgement/emotion that may be compromised in its evaluation in animals.

Instead, perhaps we should think of canine impulse-control disorder, in general, as a pathology involving both control and anxiety; the control is a direct result of the anxiety and is the rule structure by which the patient attempts to deal with and address the anxiety. In type 1 the patient is working every second to keep their reactivity level below their explosive threshold. Behaviors exhibited by humans involving manipulating the patient or the patient's access to their own behaviors function to induce the patient's reactivity to approach the threshold. Once the threshold is reached the patient fully, and often indiscriminately, "fires". In this case the "firing" results in full-blown attack. The dilation of the pupils described by the clients is a sympathetic response. That the dogs often withdraw afterwards is logical: the response is physically exhausting, as is long-standing anxiety, itself. Also, although these dogs may be uncertain about appropriate contextual responses, they are certain that their response is viewed by the humans as "wrong". These dogs may even realize that they are out of control; humans with impulse-control disorders realize that something is wrong and that their response was wrong, although they feel helpless to stop it, once started.

In type 2 of this condition the dogs use somewhat threatening behaviors to deform their social interactions involving humans. In this way the dog gets information about the individual person's response and whether the dog should worry or feel threatened, given the context. People who give the dogs clear, unambiguous signals that do not scare, injure, hurt, or threaten the dog tend to have a good relationship with the dog. People who are unclear, timid, or truly threatening are at risk from the dog because the dog has now, by deforming the social environment and getting information, confirmed the individual's unreliability. This is a rule structure that ideally should address the anxiety by telling the dog when there is a threat, but backfires because the humans don't understand what the dog is doing. All attempts to lead by physical intimidation ("dominate the dog") are teleologically doomed to failure, worsen the dog, cause increased risk of injury to humans, and may result in the dog's death.

### **A New Look at Canine Dominance Aggression - The Neurobehavioral Genetics Paradigm**

Canine dominance aggression is a control disorder that has impulsive and non-impulsive forms. Both forms involve access to control in direct social situations involving humans. The range of behaviors manifest in this condition includes postural threats and stares to sudden stiffening and bites [13,19,20]. This is the primary category of canine aggression in which no warning is given [21].

Impulsivity in humans has been relatively well studied from the behavioral aspect because of the public safety and legal concerns associated with the attendant aggression [11]; however, any behavior that is considered unduly risky or inappropriate has a tendency to be labeled "impulsive". Impulse-control disorders in humans are characterized phenotypically. Intermittent explosive disorder is characterized by failure to resist aggressive impulses that then result in explosive attacks [14]. The aggression is grossly out of proportion or out of context with any ostensible provocative stimulus. Individuals are remorseful after the event. While it is difficult or impossible to evaluate "resistance" or "remorse" in dogs, those affected with dominance aggression exhibit out-of-context, inappropriate, abnormal - whether in scope or form - behaviors under relatively non-provocative circumstances. After the outbursts these dogs often withdraw and may be avoided by other family pets.

Little work has been done either post-mortem on neuroanatomy or cytoarchitectural facets of these conditions, or ante-mortem using imaging studies of dominance aggression or impulsivity, *per se*. Limbic system structures, in general, have been related to impulsive risk-taking, behavioral timing, and time judgements [22].

The serotonin system has been implicated in both canine impulse - control disorder/dominance aggression and in human impulsivity. Affected dogs have been reported to have both lower [23] and equivalent [24] CSF levels of 5-hydroxyindol acetic acid (5-HIAA) and homovanillic acid (HVA), metabolites of serotonin and dopamine, respectively, post-mortem when compared with control dogs. Clearly, any conclusions regarding CSF levels of neurotransmitter and the condition are premature.

In a screening study seeking to examine urinary metabolites, dominantly aggressive dogs were statistically over-represented, compared with unaffected controls and all other canine patients evaluated for behavioral problems for excess excretion of certain amino acids that may be related to excitatory amino acids [25]. Further refinement of amino acid identification is still needed to interpret these findings. Afflicted dogs respond to treatment with TCAs (tricyclic antidepressants) and SSRIs (selective serotonin re-uptake inhibitors) when combined with behavior modification, supporting at some level an association between improvement and serotonin levels.

These neurochemical findings are interesting in light of the putative role of serotonin in impulsivity [26]. Linnoila et al., [27] found that CSF 5-HIAA was reduced in aggressive human patients only for those who were impulsive. This correlation between serotonin metabolites and impulsivity has been noted in further studies [28-30] that implicate low serotonin turnover rate in impulsive aggression. Treatment for many of these patients involves augmentation of serotonin through use of TCAs and SSRIs, as for dogs. Part of the problem in assessing the relative importance of such changes is that monoamine levels appear to change over the course of development in humans and over the course of the condition [31], so these data may be more relevant than they seem. Finally, monoamine levels may not accurately reflect functioning of receptors or neurons, and, as discussed below, serotonin may not be the relevant target. Instead, serotonin may be the messenger by which trophic compounds that remodel receptors are stimulated to act.

### **Considerations for the Neurobiology of Canine Obsessive-Compulsive Disorder**

The behavior changes that occur with seizures include, one or more of the following involuntary phenomenon:

1. loss or derangement of consciousness or memory (amnesia),
2. alteration of muscle tone or movement,
3. alterations of sensation and special senses including visual, auditory, and olfactory hallucinations,
4. disturbances of the autonomic nervous system (e.g., salivation, urination, defecation), and
5. other "psychic" manifestations, abnormal thought processes or moods recognized as behavioral changes (e.g., fear, rage) [16].

Unfortunately, in the absence of criteria that also require abnormal brain function characterized by paroxysmal, stereotyped alterations in behavior, and the aural, ictal, and postictal phases, these 5 suites of behavioral descriptions are sufficiently broad that all behavioral conditions could be considered related to "seizure disorders". This observation suggests, again, that the extant paradigms for understanding neurobehavioral conditions are inadequate to describe the elegant interacting neurochemical, receptor, and genomic mechanisms that specify brain function in normal and abnormal states.

Obsessive-compulsive disorder (OCD) in dogs is usually recognized because of the presence of the compulsive component - the ritualistic, stereotypic behaviors. Obsessive compulsive behaviors can include those characterized by circling, tail-chasing, flank sucking (particularly in Dobermans), fence running, fly-biting, self-mutilation (acral lick granuloma, neurotic dermatitis), hair/air biting, pica, pacing/spinning, staring and vocalizing, some aggressions, self-directed vocalizing, and wool/fabric-sucking/chewing (particularly in cats) [32,33]. Because behaviors manifest in OCD are often normal behaviors exhibited in an inappropriate, excessive, or out-of-context manner, history becomes particularly important in elucidating

whether the patient truly has OCD. Parallel examples of stereotypic behaviors are found in human medicine. These include trichotillomania (hair-pulling), hand washing, and checking (lights, gas jets, locks) [34].

Although the underlying etiology of these disorders is unclear for both dogs and humans, the symptomology and pathophysiology are striking. OCD is characterized by repetitive, ritualistic behaviors, in excess of any required for normal function, the execution of which interferes with normal, daily activities and functioning. Inherent in this description is a behavior that is exaggerated in form as well as duration. Furthermore, the behavior can be perceived by the human patient as abnormal and may be controlled to the extent that the behavior is performed only minimally, or not at all, in the presence of others. This is probably also true for domestic animals. Dogs who flank suck or tail chase may, after frequent reprimands and corrections, remove themselves from view of the owners, then commit the behavior elsewhere. Upon approach, the behavior ceases, to be begun again when no one is watching or when the animal removes himself from view. The presence of a cognitive component is not sufficient to rule out OCD, but it does suggest that the problem is rooted at a higher level than the behavior, alone, may indicate (i.e., the Doberman is flank-sucking, but not because anything is wrong with its flank). This particular class of OCD makes the case for obsessions being a valid component of OCD. We evaluate obsessions in humans by asking them about ruminant, invasive thoughts. The verbal or written component of the response is a translation of the rumination - it is not identical to the ruminant thought, itself. It is inappropriate to apply a criteria to one species that has a divergent phylogeny that prohibits the use of that tool or criteria.

Not all dogs and cats fit a volitional pattern where they can at least temporarily stop their compulsive behaviors. Some dogs show continuous stereotypic and ritualistic behavior regardless of distraction or companionship. It is not necessary that the behavior be continuously witnessed for the animal to have OCD, but it is requisite that the offending behavior substantially interfere with normal functioning in the absence of physical restraint. If the desire to exhibit the behavior is present, despite restraint because of punishment, training, or physical incarceration, the condition is present. The key is that if such control is removed and the animal could commit the behavior he will commit the behavior. Ignoring this crucial point will result in under-diagnosis of OCD and under-estimation of its frequency in canine and feline populations.

Obsessive-compulsive disorder in humans frequently appears in adolescence, and continues through mid-life. Human patients are generally clustered into four major groups: washers, checkers, ruminators, and an indistinct group of primary obsessive slowness. In dogs, OCD also appears during social maturity, and left untreated, whether by behavioral or pharmacologic intervention, it worsens.

In the case of OCD, the facets of a seizure disorder that are often concordant with the behaviors can include apparent loss or derangement of consciousness or memory (amnesia) or the appearance of confusion that the animal may perceive associated with the recurrent urges or obsessions to act in their own, peculiar stereotypic manner, alteration of movement, visual, auditory, and olfactory hallucinations, and abnormal thought processes or moods recognized as behavioral changes (e.g., fear, rage). Caution is urged here in associating unspecified and non-specific signs with either a descriptor (e.g., "rage") or a diagnosis (e.g., "fear"). Furthermore, we are severely handicapped in our ability to measure or assess auditory or olfactory alteration; we are utterly incapable of defining "psychic" manifestations in pets. Such terminology adds nothing to our knowledge and actually interferes with our ability to understand the problem by allowing us to dismiss it with a label. Disturbances of the autonomic nervous system function (e.g., salivation, urination, defecation) may be secondary to other behaviors, and should not be considered diagnostic or pathognomonic, alone. In fact, these physical, measurable, and visual non-specific signs are shared by a number of conditions, and the extent to which the animal exhibits multiple signs may hint about underlying mechanism of the disorder and about prognosis [5]. Because non-specific signs associated with all forms of OCD in both dogs and cats appear out of context to the owner and stereotyped they are often incorrectly grouped with seizure disorders.

Lick granulomas have been variously attributed to neuropathies or atopy, but we should consider that these attributions be the result of correlations of non-specific signs. Some lick granulomas have been attributed to a neuropathy/radiculopathy [137]. In these cases it is unclear if the radiculopathy is primary or secondary to the damage and lesion. This is an important point because in studies involving nerve conduction function, although some dogs with lick granulomas appeared to have aberrant nerve conduction function, the leg with the lesion was not the only leg that was affected [138]. Such data strongly suggest that problems with nerve conduction velocities are not causal in a solitary manner. At some point in their pathology these lesions appear to change in an almost chaotic way at some point and what leads to that change should be the mechanism for the pathology. The SSRIs and specific TCAs are fantastic analgesics - particularly for myopathic and neuropathic pain - because they have some effects on the dorsal root ganglia and some complex and poorly understood interaction between serotonin, nitric oxide and substance P, in addition to a host of kinin agents [139]. It is possible that when we have a lick granuloma we are actually seeing a manifestation of a bizarre migration of dysfunctional cells that, during gastrulation, experienced some regulatory inductive effects, or that are affected post-development by other neuroregulatory dysfunction

[140,141]. Hence, the behavioral (central) and peripheral signs are co-morbid. If people would begin to collect good behavioral history data so that we could more discretely define the phenotypic subgroups we might be able to test that hypothesis.

If this classification is so egregious, why does a drug commonly used to treat seizure disorders, phenobarbital, often initially aid in or mitigate the treatment of OCD?

This question elucidates the crux of the entire argument in favor of a paradigm shift to further our understanding of neurobehavioral genetics. GABA (gamma amino butyric acid) is formed from the excitatory amino acid (EEA) glutamate via glutamic acid decarboxylase (GAD), catalyzed by GABA-transaminase (GABA-T) and destroyed by transamination. There are two main groupings of GABA receptors: GABA-A and GABA-B. GABA-A receptors, ligand-gated ion channels, mediate post-synaptic inhibition by increasing chloride influx. Barbiturates and benzodiazepines are potentiators of GABA-A [35]. Both barbiturates and progesterone suppress excitatory responses to glutamate [36]. Pre-synaptic barbiturates inhibit calcium uptake and decrease synaptosomal release of neurotransmitters, including GABA and glutamate [37]. Accordingly, if both OCD and seizure activity involve dysregulation of GABA and glutamate at some level, it would not be surprising that barbiturates can affect both. OCD is a progressive disorder. It is possible that as the condition progresses other neurochemical tracts (e.g., those in the dorsal raphe affecting serotonin) become involved with resultant dysfunction of serotonin metabolism. At this point, barbiturates, which provided an initial, relatively non-specific neuromodulatory role, are insufficient to address the level and form of neurochemical pathology. The barbiturates would then be said to work "some of the time" or "early". Uncritical acceptance of such statements tricks us to thinking we understand something when, in fact, the chance for further understanding has been obscured.

### **A New Look at Canine OCD - The Neurobehavioral Genetics Paradigm**

Studies involving computed tomography have implicated the basal ganglia, particularly in the region of the basal ganglia and the caudate nucleus [38-41]. These regions have also been implicated in animal models [42,43]. Changes in cerebral glucose metabolism in the orbitofrontal region have been found to correlate response to treatment [25]. The pathology of OCD appears to be partially attributable to aberrant serotonin metabolism, although some have postulated a tandem role for abnormal endorphin metabolism [44]. Neuropharmacological approaches to therapy have sought to address these abnormalities by augmenting serotonin through the use of TCAs and SSRIs [45]. A complete understanding of the integrated anatomical and neurophysiological mechanisms of OCD is not yet a reality.

As is true for humans, OCD appears to be rooted in a neurophysiological abnormality [33], and dogs respond well to the tricyclic antidepressant clomipramine [33,46-49] and to the SSRI, fluoxetine [50]. In dogs, as in humans, in the absence of behavioral and pharmacological treatment, OCD rarely resolves. Should the medication be discontinued, the patient relapses in many cases [13]. Symptoms may be worse or more pronounced in stressful or anxiety producing circumstances [14,15].

It has been hypothesized that there is a genetic and heritable component to the condition since it appears to run in some family lines; at least 2 - 3% of the general human population is afflicted with obsessive-compulsive disorders. First degree relatives have a greater risk for the condition than do members of families in the unaffected human population. Given that dog breeds represent genetic canalization that is further compounded by inbreeding schemes, we would expect the incidence in the canine population to be higher than that in the human population. The breeds in which OCD appears to run in family lines that are commonly seen in the Behavior Clinic at VHUP are: great Danes, German short-haired pointers, German shepherd dogs, bull terriers [48], English bull dogs, Jack Russell terriers, Dalmatians, Bouvier de Flanders, Salukis, Cairn terriers, basset hounds, and soft-coated Wheaten terriers [51]. As is true for humans, first degree relatives usually have a different manifestation of OCD than does the proband. These features support the above hypotheses of a neurochemical/neurogenetic basis for OCD. Again, it is important to remember that although this condition responds to TCAs and SSRIs (e.g., compounds affecting serotonin), augmentation of serotonin may not be the end point. Serotonin may function only to trigger 2nd messenger systems that then affect transcription and translation of proteins that comprise receptors, as discussed later.

### **Considerations for the Neurobiology of Canine Cognitive Dysfunction**

Cognitive dysfunction is broadly defined in animals to represent geriatric behavioral changes not attributable to a general medical condition [13,52]. This definition encompasses all of the human geriatric dementias and is not sufficiently specific to delineate a sub-population that may be a good phenotypic model for anxiety. The commonly noted signs of cognitive dysfunction are similar to those noted for canine separation anxiety: elimination in the house and alterations in activity level. The pattern of these changes differs from that seen in true separation anxiety dogs, and the dogs also exhibit behaviors consistent with disorientation that may share similarities with some of the behavioral changes associated with seizure disorders.

Finally, in dogs such signs can be difficult to separate from non-specific changes associated with decreasing function of the visual, auditory, or locomotor systems that occurs with aging. There are currently few published assessment scales that permit objective evaluation of behavioral changes either with the progress of the condition(s) or with treatment (but see [53]). Thus far, the majority of data have been collected from opinion surveys of owners. This is an inadequate and insufficient tool, and is neither reliable nor repeatable. Future work in the field needs to address quantification and qualification of the specific behaviors noted in cognitive dysfunction.

Age-related memory dysfunction is extraordinarily difficult to assess in dogs, but it can and has been done using longitudinal studies of actual behavioral progressions and changes and responses to provocative memory tests are required to enhance specificity of behavioral correlates and diagnosis [54-56].

### **A New Look at Canine Cognitive Dysfunction - The Neurobehavioral Genetics Paradigm**

As is true with human Alzheimer's disease, definitive diagnosis may be ascertainable only post-mortem [57]. Aged dogs with cognitive changes show similar lesions, including the deposition of  $\beta$ -amyloid plaques to those seen in human patients [58]. The hippocampus and the cerebral cortex are primarily affected [58,59], as is true for most humans. Additional changes include ventricular dilation, thickening of the meninges, vascular changes, and reactive gliosis [60,61]. Caution is urged about attributing too much weight to such changes: they can be non-specific and may occur in a number of neurodegenerative disorders, as well as in unaffected patients without cognitive signs [62-64]. A study of cognitively unimpaired aged humans found that 51 of 59 subjects had neurofibrillary tangles post-mortem and 46 of 59 subjects had diffuse neuritic, senile plaques throughout the neocortex and entorhinal cortex, and vascular amyloid was present in 44 subject [63].

Imaging studies in humans have also produced somewhat non-specific results. Ventricle-to-brain ratio appears to be larger in manic geriatric patients compared with controls [65], but this is not directly associated with age nor does it correlate well with cortical sulcal widening. Cortical sulcal widening was larger in geriatric manic patients when compared with age-matched controls [65,66]. Again, a strong argument can be made for further, more specific investigation.

Treatment with selegiline (L-deprenyl) has a beneficial effect in laboratory tests of aged canine cognitive performance [67,68] that mirrors improvements similar to those seen in the treatment of Parkinson's disease [69,70]. This effect may be a non-specific and related to augmentation of dopamine via direct effects in the pre-synaptic neuron, or indirect effects on other biogenic amines and neuromodulation.

Apolipoprotein studies suggest that some forms of human Alzheimer's disease may be genetically affected. There are no comparable studies in dogs currently; however, in laboratory beagles a congruence of pathology was found within 15/16 litters [71]. There are few data available for dogs concerning regulatory or structural proteins that have been implicated in normal or pathological brain or in neurological or neuropsychiatric conditions. In humans, synaptic proteins involved in structural plasticity and remodeling of axons and dendrites, debrin [post-synaptic] and GAP-43 [-neuromodulin; pre-synaptic] decline significantly with normal aging [72]. We know that neuroregulatory proteins are involved in the pathology of both human [73] and canine narcolepsy, and that the molecular genetics of the defect associated with neuromodulatory/neuroregulatory dysfunction differs between afflicted breeds [74,75]. This system, in turn, is affected by activation of the histaminergic system. Obviously, regulatory issues are complex and have complex effects on phenotypes, including those associated with cognition, in general, and its various declines. Paradigms seeking to understand associations between neurological attributes and behaviors must accommodate these complex issues.

### **General Associations Between Neurobehavioral Genetics, Neuroanatomy, and Fears and Anxieties**

The specific neuroanatomy of a fear response involves the locus coeruleus (LC), the principal norepinephrinergic (noradrenergic) nucleus in the brain. Dysregulation of the LC appears to lead to panic and phobias in humans [77]. The LC directly supplies the limbic systems and may be responsible for many correlated "limbic" signs. Patients with true panic and phobic responses are more sensitive to pharmacologic stimulation and suppression of the LC than controls [77-79].

The hypothalamic-pituitary-adrenal (HPA) axis has been implicated in anxiety and other disorders. Researchers have variously reported hypercortisolemia and flattening of responses in patients with panic [80-82], suggesting that this is another condition that is heterogeneous.

Positive emission tomography (PET) scans have been used to study regional brain blood flow: increases in blood flow in bilateral temporal poles during anticipatory anxiety have been noted, as has an asymmetry of cerebral blood flow (left < right) in the parahippocampal gyrus [83,84]. The lactate test is an accepted test to provoke (and diagnose) panic attacks in people, but until recently it had not been evaluated in dogs [85]. In human lactate-responsive/susceptible patients, parahippocampal blood flow (a marker of neuronal activity), blood volume, and oxygen metabolism are asymmetric when evaluated by PET scans under resting, non-panic conditions. This suggests that the abnormality is both biochemical and structural. The biochemical abnormality is postulated to be due to an increase in norepinephrine output from the locus coeruleus, which, in turn, stimulates parahippocampal "over-responsiveness". The behavioral and physiological responses to



the lactate test are sufficiently promising that similar imaging studies should be done in animals.

Recently, a role for abnormal serotonin function has been substantiated, in part, based on the shared ontogeny and amygdaloid projections of serotonin neurons and those associated with the LC [86]. In this system serotonin is postulated to have a modulatory role that directly or indirectly affects discharge of brain stem nuclei, limbic activation, and prefrontal cortex activation. Such models of complexity and inter-regulation are likely to more closely explain the mechanistic variability underlying population heterogeneity in conditions like panic disorder. Further evidence implicating both serotonergic neurons and benzodiazepine receptors comes from the clinical literature demonstrating the efficacy of TCAs, SSRIs, and benzodiazepines in the treatment of panic disorder and related anxieties [87-97].

#### **Hints About Genetics of Anxiety from Rodents**

Rats bred for high (HAB) or low anxiety-related behaviors (LAB) have provided some insight into possible genetic mechanisms involved in panic disorder. Despite similar basal levels of ACTH and corticosterone HAB rats show higher plasma concentrations at both 5 and 15 minutes after provocative testing and have higher basal and stimulated levels of prolactin than do LAB rats [98]. Transgenic mice that over-produce corticotropin releasing factor (CRF) show increased anxiety-related behaviors that are reversed by central administration of a specific CRF antagonist, suggesting a neuromodulatory role for CRF in the regulation of stress and anxiety [99]. The *Drosophila* white gene shares significant sequence similarity to a gene regulating tryptophan found on human chromosome 21 (21q22.3); associations between gene polymorphism and mood and panic disorders were significant for human males, suggesting that this gene may at least partially control mood, anxiety, and panic disorders [100].

#### **Anxiety and Related Psychopharmacology - A Preliminary Caution**

The use of medication should occur and is most effective as part of an integrated treatment program. There is no substitute for the hard work involved in behavior modification; however, some medications may be able to make it easier to implement the modification [101]. Those seeking "quick fix" solutions will doubtless be disappointed: inappropriate drug use will only blunt or mask a behavior without alteration of processes or environments that produced the behavior. Furthermore, the newer, more specific, more efficacious drugs have a relatively long lag time between initiation of treatment and apparent changes in the patient's behavior. This delay is due to the mechanism of action of the TCAs and SSRIs which employ second messenger systems to alter transcription of receptor proteins. The primary focus is on the main groups of drugs now recommended for use: those drugs affecting serotonin and GABA.

#### **Neurotransmitters and Neurochemical Tracts**

The neurotransmitters affected by behavioral medications are acetylcholine, serotonin, norepinephrine (noradrenaline), dopamine, GABA, and excitatory amino acids. Common adverse effects of psychotherapeutic drugs are usually caused by a blockage of the muscarinic acetylcholine receptors, which have diffuse connections throughout the brain.

Serotonin (5-hydroxy-tryptamine [5-HT]) - Serotonin receptors are all G-protein-coupled receptors. There are 14 identified classes of serotonin receptors. The 5-HT<sub>1</sub> receptors are linked to the inhibition of adenylate cyclase and affect mood and behavior. Presynaptic 5-HT-1A receptors predominate in dorsal and median raphe nuclei; post-synaptic 5-HT-1A receptors are predominant in limbic regions (hippocampus and septum) and some cortical layers. Activation of pre-synaptic receptors by agonists results in decreased firing of serotonergic neurons leading to transient suppression of 5-HT synthesis and decreased 5-HT release; activation of post-synaptic receptors decreases firing of post-synaptic cells. These are homeostatic effects, not integrated outcomes of receptor activation. The overall effect depends on regulation of second messengers (cAMP, Ca<sup>++</sup>, cGMP, IP<sub>3</sub>) and their effects on protein kinases which then alter neuronal metabolism and receptor protein transcription. The subclasses of 5-HT receptors vary in their effects. 5-HT-1A receptors affect mood and behavior. 5-HT-1D receptors affect cerebral blood vessels and appear to be involved in the development of migraine.

Noradrenaline/norepinephrine (NE) - The most prominent collection of noradrenergic neurons is found in the locus coeruleus of the gray matter of the pons and in the lateral tegmental nuclei. There is also a cluster in the medulla. NE has been postulated to affect:

1. mood (decreases in depression and increases in mania),
2. functional reward systems, and
3. arousal.

Dopamine - The distribution of dopamine in the brain is non-uniform, but is more restrictive than that of NE. Dopaminergic nuclei are found primarily in:

1. the substantia nigra pars compacta which projects to the striatum and is largely concerned with coordinated movement;
2. the ventral tegmental area which projects to the frontal and cingulate cortex, nucleus accumbens, and other limbic structures; and
3. the arcuate nucleus of the hypothalamus which projects to the pituitary. A large proportion of the brain's dopamine is found in the corpus striatum, the part of the extrapyramidal system concerned with coordinated movement.

Dopamine is metabolized by monamine oxidase (MAO) and catechol-O-methyl transferase (COMT) into dihydroxyphenyl acetic acid (DOPAC) and homovanillic acid (HVA). HVA is used as a peripheral index of central dopamine turnover in humans, but this use has been little explored in veterinary medicine. All dopaminergic receptors are G-protein-coupled transmembrane receptors. The D-1 receptors exhibit their post-synaptic inhibition in the limbic system and are affected in mood disorders and stereotypies. The D-2, D-3, and D-4 receptors are all affected in mood disorders and stereotypies. Excess dopamine, as produced by dopamine releasing agents (amphetamines and dopamine agonists, like apomorphine) is associated with the development of stereotypies.

Gamma Amino Butyric Acid (GABA) - GABA, the inhibitory neurotransmitter found in short interneurons, is produced in large amounts only in the brain and serves as a neurotransmitter in ~30% of the synapses in the human CNS. The only long GABA-ergic tracts run to the cerebellum and striatum. GABA, formed from the EEA glutamate, has two main groupings of receptors: GABA-A and GABA-B. GABA-A receptors, ligand-gated ion channels, mediate post-synaptic inhibition by increasing Cl<sup>-</sup> influx. Barbiturates and benzodiazepines are a potentiators of GABA-A. GABA-B receptors are involved in the fine-tuning of inhibitory synaptic transmission: presynaptic GABA-B receptors inhibit neurotransmitter release via high voltage activated Ca<sup>++</sup> channels; postsynaptic GABA-B receptors decrease neuronal excitability by activating inwardly rectifying K<sup>+</sup> conductance underlying the late inhibitory post synaptic potential [36].

GABA also has a variety of tropic effects on developing brain cells [102]. During ontogeny GABA-ergic axons move through areas where other neurotransmitter phenotypes are being produced, and so may be related to later monoaminergic imbalances [36]. Whether the extent of such ontogenic effects are relevant for behavioral conditions is currently unknown but bears investigating.

EAAs (glutamate, aspartate, and, possibly, homocysteate) - EAAs have a role as central neurotransmitters and are produced in abnormal levels in aggressive, impulse, and schizophrenic disorders. The main fast excitatory transmitters in the CNS are EAAs. Glutamate, widely and uniformly distributed in the CNS, is involved in carbohydrate and nitrogen metabolism. It is stored in synaptic vesicles and released by Ca<sup>++</sup> dependent exocytosis, so calcium channel blockers may affect conditions associated with increased glutamate. Both barbiturates and progesterone suppress excitatory responses to glutamate [37]. Pre-synaptic barbiturates inhibit calcium uptake and decrease synaptosomal release of neurotransmitters, including GABA and glutamate [38].

Other Chemical Mediators - Nitric oxide (NO) and arachidonic acid metabolites (e.g., prostaglandins) can mediate neurotransmitter release. These are synthesized on demand and released by diffusion, requiring no specialized vesicles or receptors. Like encapsulated neurotransmitters (i.e., ACh) that are extruded through exocytosis after binding with the synaptic membrane, these chemical mediators are activated by an increase in calcium, so may be affected by calcium channel blockers.

### **Classes of Drugs Used and Misused in Behavioral Medicine**

Anti-histamines, anti-convulsants, progestins/estrogens, sympathomimetics/stimulants, narcotic agonists/antagonists, and mood stabilizers/antipsychotics have been discussed elsewhere [15]. With the exception of the last class they have limited use in modern behavioral medicine. The focus here is on the medications affecting GABA and 5-HT: the benzodiazepine tranquilizers, MAO-Is, TCAs, SSRIs, and 5-HT agonists.

Tranquilizers - Tranquilizers decrease spontaneous activity, resulting in decreased response to external or social stimuli. They interfere profoundly with any behavioral modification. Neuroleptic butyrophenones like haloperidol decrease both appropriate and inappropriate activity, and because of side effects associated with the most effective mode of delivery (i.e., IV), have limited use. Use of phenothiazines (e.g., chlorpromazine, promazine, acetylpromazine, and thioridazine), which

target the dopamine receptor, is outdated, the level and duration of tranquilization varies and both normal and abnormal behaviors are blunted. All phenothiazines have side effects from long standing use (e.g., cardiovascular disturbance, extrapyramidal signs). Acetylpromazine makes animals more reactive to noises and startle, and so is wholly inappropriate for use in noise phobic patients.

The exact mechanism of action of the benzodiazepines (e.g., diazepam, chlordiazepoxide, clorazepate, lorazepam, alprazolam, and clonazepam) is poorly understood. Calming effects may be due to limbic system and reticular formation effects. Compared with barbiturates, cortical function is relatively unimpaired by benzodiazepines. All benzodiazepines potentiate the effects of GABA by increasing binding affinity of the GABA receptor for GABA and increasing the flow of chloride ions into the neuron, affecting primarily GABA-A receptors. Barbiturates also affect the GABA receptor-benzodiazepine receptor-chloride ion channel complex, but because of detrimental effects on cognition barbiturates have been superseded by benzodiazepines and TCAs in the treatment of aggression. Binding of diazepam is highest in the cerebral cortex compared with the limbic system and midbrain, which are, in turn, higher than the brainstem and the spinal cord, paralleling the distribution of GABA-A receptors.

At low dosages, benzodiazepines act as mild sedatives, facilitating daytime activity by tempering excitement. At moderate dosages they act as anti-anxiety agents, facilitating social interaction in a more proactive manner. At high dosages they act as hypnotics, facilitating sleep. Ataxia and profound sedation usually only occur at dosages beyond those needed for anxiolytic effects. Benzodiazepines decrease muscle tone by a central action that is independent of the sedative effect, but may function as a non-specific anxiolytic effect. Some newer benzodiazepines like clonazepam have muscle relaxation effects at smaller dosages than those needed for behavioral effects. Many of the long-term effects and side effects of benzodiazepines are the result of intermediate metabolite function. Parent compound and intermediate metabolite  $t_{1/2}$  are found in Table 5 for humans and Table 6 for domestic species [103,104].

**Table 5. Half-lives of Parent Compounds and Intermediate Metabolites of Target Benzodiazepines in Humans**

Parent Compound	$t_{1/2}$ Parent Compound	$t_{1/2}$ Intermediate Metabolite	Overall Duration of Action
Triazolam	2 - 4 h	2 h	Ultra Short: 6 h
Oxazepam	8 - 12 h	---	Short: 12 - 18 h
Alprazolam	6 - 12 h	6 h	Medium: 24 h
Diazepam	24 - 40 h	60 h	Long: 24 - 48 h
Clonazepam	50 h	---	Long: 24 - 48 h

**Table 6. Duration of Action of Parent Compound, Diazepam, and its Intermediate Metabolite, Nordiazepam (N-desmethyl Diazepam) in Selected Domestic Animals [104]**

Species	Diazepam	N-desmethyl diazepam	Oxazepam [103]
Horse	24 - 48 h	51 - 120 h	---
Cat	5.5 h	21 h	---
Dog	3.2 h (if given PO) 0.258 h (if given IV)	3 - 6 h (if given PO) 2.20 h (if given IV) 2.83 h (if given rectally)	3.83 h (if given IV) 5.13 (if given rectally)

Benzodiazepines are essential for treatment of sporadic events involving profound anxiety or panic (e.g., thunderstorms, fireworks, panic associated with departures of humans signaled by an outside indicator, e.g., an alarm clock). For these drugs to be efficacious they must be given to the patient at least an hour before the anticipated stimulus, and minimally before the patients exhibit signs of distress. This timing allows repeat dosing that makes use of the  $t_{1/2}$  of parent compounds and intermediate metabolites and permits concomitant use with daily TCA or SSRI treatment.

Monoamine oxidase inhibitors (MAO-Is) - MAO-Is act by blocking oxidative deamination of brain amines (dopamine, norepinephrine, epinephrine, 5-HT), increasing these substances, and elevating mood. The MAO-B inhibitor, selegiline is used to treat "cognitive dysfunction" in aged cats and dogs, but in dogs deamination of catecholamines is controlled by MAO-A. Selegiline is fairly specific for dopamine and slows destruction of synaptic knobs of presynaptic neurons.

TCAs - TCAs are structurally related to the phenothiazine antipsychotics. In humans they are commonly used to treat endogenous depression, panic attacks, phobic and obsessive states, neuropathic pain states, and pediatric enuresis. The antidepressant effect is due to inhibition of prejunctional re-uptake of norepinephrine and serotonin. There are three major effects of TCAs that vary in degree depending on the individual drug:

1. sedation,
2. peripheral and central anticholinergic action, and
3. potentiation of CNS biogenic amines by blocking their re-uptake presynaptically.

The ability of TCAs to inhibit prejunctional re-uptake of norepinephrine and serotonin is largely responsible for their antidepressant effect. Many TCAs also have potent muscarinic,  $\alpha$ 1-adrenergic, and H-1 and H-2 blocking activity, which can account for their common side effects (dry mouth, sedation, hypotension). The H-1 and H-2 effects, however, may be useful in treating pruritic conditions (e.g., doxepin).

The tertiary amines (amitriptyline, imipramine, doxepin, trimipramine, and clomipramine) are metabolized to secondary amines (desipramine, nortriptyline, and protriptyline). These classes of anti-depressants are among the most widely and safely (compared with benzodiazepines, phenothiazines, barbiturates, and sympathomimetic agents) used drugs in companion animal behavioral medicine.

In general, TCA metabolites are more potent inhibitors of NE uptake, while parent compounds are more potent inhibitors of 5-HT uptake; metabolites usually have similar or longer half-lives compared with the parent compound. Imipramine's intermediate metabolite, norimipramine, is a more potent inhibitor of NE uptake than is imipramine (it is also an active intermediate metabolite of other anti-anxiety agents) and has its own active intermediate metabolite. Doxepin's intermediate metabolite, nordoxepin, fully retains the pharmacological properties of the parent compound, and its  $t_{1/2}$  is 33 - 88 h in humans compared with a  $t_{1/2}$  of 8 - 25 h with doxepin. Norclomipramine (N-desmethyloclopramine), one of the active intermediate metabolites of clomipramine, is also a more potent inhibitor of NE than is clomipramine and has an elimination  $t_{1/2}$  1.5 times longer than that of clomipramine [105]. Not only does this have profound implications for calculating how long one expects effects to last, but it is interesting to note that the ability to formulate intermediate metabolites is subject to genetic polymorphism in the human population. One can only imagine the complexity for the canine and feline populations. Most dogs treated with clomipramine (Clomicalm, Novartis Animal Health) reach steady state levels in 3 - 5 days, attain peak plasma concentrations in approximately 1 - 3 h, and experience  $t_{1/2}$  of 1 - 16 h of the parent compound and 1 - 2 h of the active intermediate metabolites [101,106], suggesting that dogs may require higher dosages or more frequent dosing than do humans treated with such medications.

Knowledge of intermediate metabolites can be important: animals experiencing sedation or other side effects with the parent compound may do quite well when treated with the intermediate metabolite, alone. For example, cats that become sedated or nauseous when treated with amitriptyline may respond well when treated with nortriptyline at the same dose. Table 7 lists parent compounds, intermediate metabolites, and their relative effects on NE and 5-HT. Side effects in humans can include a dry mouth, constipation, urinary retention, tachycardias and other arrhythmias, syncope associated with orthostatic hypotension and  $\alpha$ -adrenergic blockade, ataxia, disorientation, and generalized depression and inappetence [107]. Symptoms usually abate upon decrease or cessation of drug administration.

Use of TCAs is contraindicated in animals with a history of urinary retention and severe, uncontrolled cardiac arrhythmias [109] and a cardiac consult, including a rhythm strip, should be a part of standard, pre-dispensation work-up. The common side-effects of TCAs as manifest on ECG include: flattened T waves, prolonged Q-T intervals, and depressed S-T segments. In high doses TCAs have been implicated in sick euthyroid syndrome. In older or compromised animals complete laboratory evaluations are urged since high doses of TCAs are known to alter liver enzyme levels. Extremely high doses are associated with convulsions, cardiac abnormalities, and hepatotoxicity. TCAs can interfere with thyroid medication necessitating conscientious monitoring if administration of both medications is concurrent. Cats are likely to be more sensitive to all TCAs than are dogs because TCAs are metabolized through glucuronidation.

TCAs are extremely successful in treating many canine and feline conditions including separation anxiety, generalized anxiety that may be a precursor to some elimination and aggressive behaviors, pruritic conditions that may be involved in acral lick dermatitis (ALD), compulsive grooming, and some narcoleptic disorders. Amitriptyline is very successful in

treating separation anxiety and generalized anxiety. Imipramine has been useful in treating mild attention deficit disorders in people, and may be useful in dogs since it has been used to treat mild narcolepsy. Clomipramine has been inordinantly successful in the treatment of human and canine obsessive compulsive disorders [34,46-48,110-115]. Clomipramine has one active, intermediate metabolite, clomipramine, that acts as a serotonin re-uptake inhibitor [46,115].

Table 7. Relative Effects of TCA Parent Compounds and Intermediate Metabolites on NE and 5-HT Re-uptake [108]			
Parent Compound	Intermediate Metabolite	NE	5-HT
Desipramine	---	++	+
Imipramine	Desipramine	+++	++
Amitriptyline	Nortriptyline	++	++
Nortriptyline	---	+	+
Clomipramine	N-desmethyl Clomipramine + Clomipramine*	++	+++

\* does not include the specific effect of the intermediate metabolite as a selective serotonin reuptake inhibitor (SSRI).

**Serotonin Agonists** - Partial 5-HT-1A/B agonists (e.g., buspirone) have few side effects, do not negatively affect cognition, allow rehabilitation by influencing cognition, attention, arousal, and mood regulation, and may aid in treating aggression associated with impaired social interaction. Buspirone has been used with varying, but unimpressive success, in the treatment of canine aggression of dominance or idiopathic origins, canine and feline ritualistic or stereotypic behaviors, self-mutilation and possible obsessive compulsive disorders, thunderstorm phobias, and feline spraying, in a multi-cat household. Its best use is for the treatment of spraying if one of the intents is to make a victimized cat more assertive.

**SSRIs** - The SSRIs (fluoxetine, paroxetine, sertraline, and fluvoxamine) are derivatives of TCAs. These drugs have a long half-life, and after 2 - 3 weeks plasma levels peak within 4 - 8 hours. Treatment must continue for a minimum of 6 - 8 weeks before a determination about efficacy can be made since these drugs act to induce receptor conformation changes, an action that can take 3 - 5 weeks. Most of the SSRI effects are due to highly selective blockade of the re-uptake of 5-HT<sub>1</sub>-A into pre-synaptic neurons without effects on NE, dopamine, acetylcholine, histaminic, and alpha-adrenergic receptors. The SSRIs should not be used with MAO-Is because of risks of serotonin syndrome [116].

Fluoxetine is efficacious in the treatment of profound aggressions, animal models of obsessive-compulsive disorders (wheel running, anorexia, weight loss) [117], companion animal separation anxiety [118], panic, avoidance disorders, including post-traumatic stress disorder [119], and obsessive-compulsive disorders. Paroxetine is efficacious in the treatment of depression, social anxiety, and agitation associated with depression [120]. Sertraline is useful particularly for generalized anxiety and panic disorder [121].

Most of the effect of fluoxetine seems to be via a highly selective blockade of the re-uptake of 5-HT into pre-synaptic neurons. Fluoxetine appears to have no effects on NE or dopamine, no anticholinergic, no antihistaminic, and no anti- $\alpha$ -adrenergic activities, so most of the side effects associated with anti-depressants are absent or minimized. Concomitant use of TCAs or benzodiazepines increases the plasma levels of these and may prolong the excretion of fluoxetine. Co-administration of buspirone may decrease the efficacy of buspirone and potentiate extrapyramidal symptoms, but there have also been reports of synergistic effects. Fluoxetine should not be used with MAO-Is. Table 8 contains an algorithm for the "gestalt" of TCA and SSRI use. This algorithm is extrapolated from the human literature based on the similarity of dogs and humans with respect to pharmacokinetics and pharmacodynamics when treated with TCAs or SSRIs.

Acceleration of the treatment effect of TCAs and SSRIs can be accomplished by the addition of the  $\beta$ -adrenergic antagonists, pindolol, which blocks the pre-synaptic/somatodendritic autoreceptor thereby aborting the initial down-regulation phase of monoamine release [115,122].

**Table 8. "Gestalt" of TCA and SSRI Use Based on t-1/2 of Parent Compounds and Active Intermediate Metabolites, Relative Effects on NE and 5-HT, and Extrapolations from Multi-center Human Studies**

Diagnosis/Type of condition	First drug of choice
Narcolepsy	Imipramine
Milder, relatively non-specific anxieties	Amitriptyline
Milder, relatively non-specific anxieties with avoidance of sedation	Nortriptyline
Social phobias/anxieties concerning social interaction	Paroxetine
Panic/generalized anxiety	Sertraline
Outburst aggression/related anxieties	Fluoxetine
Ritualistic behavior associated with anxiety, including OCD	Clomipramine

### **Mechanism of Action of Serotonergic Agents - Why a Mechanistic Paradigm Shift is Necessary**

What makes TCAs and SSRIs special and why are they so useful for anxiety disorders? The key to the success of these drugs is that they utilize the same second messenger systems and transcription pathways that are used to develop cellular memory or to "learn" something. This pathway involves cAMP, cytosolic response element binding protein (CREB), brain derived neurotrophic factor (BDNF), NMDA receptors, protein tyrosine kinases (PTK) - particularly Src - which regulate activity of NMDA receptors and other ion channels and mediates the induction of LTP (long-term potentiation = synaptic plasticity) in the CA1 region of the hippocampus [123-125].

There are two phases of TCA and SSRI treatment: short-term effects and long-term effects. Short-term effects result in a synaptic increase of the relevant monoamine associated with re-uptake inhibition. The somatodendritic autoreceptor of the pre-synaptic neuron decreases the firing rate of that cell as a homeostatic response. Regardless, there is increased saturation of the post-synaptic receptors resulting in stimulation of the  $\beta$ -adrenergic coupled cAMP system. cAMP leads to an increase in PTK as the first step in the long-term effects. PTK translocates into the nucleus of the post-synaptic cell where it increases CREB, which has been postulated to be the post-receptor target for these drugs. Increases in CREB lead to increases in BDNF and tyrosine kinases (e.g., trkB) which then stimulate mRNA transcription of new receptor proteins. The altered conformation of the post-synaptic receptors renders serotonin stimulation and signal transduction more efficient [115,122].

Long-term treatment, particularly with the more specific TCAs (e.g., clomipramine) and SSRIs, employs the same pathway used in LTP to alter receptor function and structure through transcriptional and translational alterations in receptor protein. This can be thought of as a form of in vivo "gene therapy" that works to augment neurotransmitter levels and production thereby making the neuron and the interactions between neurons more coordinated and efficient. In some patients short-term treatment appears to be sufficient to produce continued "normal" functioning of the neurotransmitter system. That there are some patients who require life-long treatment suggests that the effect of the drugs is reversible in some patients, further illustrating the underlying heterogeneity of the patient population considered to have the same diagnosis.

### **Pre-medication Considerations**

Prior to incorporating behavioral pharmacology into any treatment program the following conditions must be met:

1. A reasonable diagnosis or a list of diagnoses should be formulated. This is different from a list of non-specific signs.
2. The clinician should have some insight into the neurochemistry relevant to the condition.
3. The clinician should have an appreciation for the putative mechanism of action of the chosen medication.
4. The clinician should have a clear understanding of any potential side effects.
5. The clinician and client should have some clear concept of how the prescribed drug will alter the behavior in question. The latter is critical because it will help clients to watch for side-effects and improvements and can help the clinician confirm or reject the diagnosis.

Without these five guidelines, behavioral drugs may not be given long enough or at a sufficient dosage to attain the desired effect, the clients will be unable to participate in the evaluation process, there will be no objective behavioral criteria that will allow the veterinarian to assess improvement, and drug selection is liable to be similar to alchemy.

Prior to prescribing any drug a complete behavioral and medical history should be taken. Should the animal be older, suffer from any metabolic or cardiac abnormalities, or be on any concurrent medical therapy, caution is urged. All animals should have complete laboratory and physical examinations. Most behavioral drugs are metabolized through renal and hepatic pathways so knowledge of baseline values is essential. For example, SSRIs are often considered "safer" than many TCAs, but because of the small sizes of clinical trials necessary to bring drugs to market the exact incidence of potential side effects is often unknown in the absence of post-marketing surveillance.

Baseline ECGs are recommended for in any patient who has had a history of any arrhythmia, heart disease, prior drug reactions, is on more than one medication, and who may be undergoing anesthesia or sedation [109]. Liver dyscrasias and cardiac arrhythmias may not rule out the use of a drug, but knowing that they exist can serve as a guide to dosage and anticipated side effects. Once alerted to potential adverse reactions clients are extremely willing to comply with all monitoring and with the extensive communication needs of behavioral cases. Clients should receive a complete list of all potential adverse responses and should be encouraged to communicate with the clinician at the first sign of any problem. Clients are often very distressed after a behavioral consultation and need a written reminder of situations for which they should be alert.

In the USA, extra-label use of human drugs, including psychopharmacological agents, for the treatment of pets hinges on a valid client/veterinarian/patient relationship. This means that a behavioral history was taken, a tentative diagnosis was formulated, and a treatment plan was developed. If any veterinarian is uncomfortable with complying with these guidelines, they should refer their behavioral cases to a specialist in behavioral medicine. Consultations directly with a client by fax, phone, mail, or e-mail, in the absence of actual visual inspection of the patient, most often do not meet the criteria of a valid client/veterinarian/patient relationship. Caution is urged. The preferred mode of consultation if the clinician can not have a visual inspection of the patient is for the consultation to take place directly with the specialist and the referring clinician, who is then responsible for treatment and follow-up.

Finally, the client household must be considered when the decision to use behavioral drugs is made. Substance abuse is rampant in humans and many drugs used for behavioral pharmacology have high abuse potential.

### **Monitoring**

Monitoring of side-effects is critical for any practitioner dispensing behavioral medication. The first tier of this involves the same tests mandated in the pre-medication physical and laboratory evaluation. Age-related changes in hepatic mass, function, blood flow, plasma drug binding, etc., cause a decrease in clearance of some TCAs, so it is prudent to monitor hepatic and renal enzymes annually in younger animals, biannually in older, and always as warranted by clinical signs. Adjustment in drug dosages may be necessary with age.

### **Withdrawal from Medication**

It is preferable to withdraw most patients from one class of drug before starting another. For changing between SSRIs and MAO-Is the recommended drug-free time in humans and dogs is two weeks (2 + half-lives: the general rule of thumb for withdrawal of any drug). SSRIs can be added to TCAs and may then exhibit a faster onset of action than when they are given alone. This is due to the shared molecular effects on second messenger systems of both TCAs and SSRIs. Combination treatment allows the clinician to use the lower end of the dosage for both compounds which minimizes side effects while maximizing efficacy. Furthermore, benzodiazepines can be used to blunt or prevent acute anxiety-related outbursts on an as needed basis in patients for whom daily treatment with a TCA or an SSRI is ongoing. Together, the combination of benzodiazepines and TCAs/SSRIs may hasten improvement and prevent acute anxiety-provoking stimuli from interfering with treatment of more regularly occurring anxieties.

When stopping a drug, weaning is preferred to stopping abruptly. A model for how to do this is found in Table 9. Weaning minimizes potential central withdrawal signs, and allows determination of the lowest dosage that is still effective [5,15]. Long-term treatment may be the rule with many of these medications and conditions, however, maintenance may be at a considerably lower level of drug than was prescribed at the outset. The only way the practitioner will discover if this is so, is to withdraw the medication slowly.

**Table 9. Algorithm for Treatment Length and Weaning Schedule**

<p><b>1-</b> Treat for as long as it takes to begin to assess effects  7 - 10 days for relatively non-specific TCAs  3 - 5 weeks minimum for SSRIs and more specific TCAs  <b>PLUS</b></p> <p><b>2-</b> Treat until "well" and either have no signs associated with diagnosis or some low, consistent level  Minimum of another 1 - 2 months  <b>PLUS</b></p> <p><b>3-</b> Treat for the amount of time it took you to attain the level discussed in (2) so that reliability of assessment is reasonably assured  Minimum of another 1 - 2 months  <b>PLUS</b></p> <p><b>4-</b> Wean over the amount of time it took to get to (1) or more slowly. Remember, if receptor conformation reverts it may take 1+ months to notice the signs of this. While there are no acute side effects associated with sudden cessation of medication, a recidivistic event is a profound "side effect". Full-blown recidivistic events may not be responsive to re-initiated treatment with the same drug and, or the same dose.  7 - 10 days for relatively non-specific TCAs  3 - 5 weeks minimum for SSRIs and more specific TCAs</p> <p><b>TOTAL:</b> Treat for a minimum of 4 - 6 months</p>
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### **Conclusions - Lessons from Schizophrenia - Humans as Models for Complex Neurobehavioral Conditions in Dogs**

Advances in treatment in behavioral medicine will be genetic, molecular, and pharmacological. We can best learn some of the pitfalls of trying to understand multi-factorial, heterogeneous disorders by comparison with the human experience with schizophrenia. Schizophrenia has been increasingly recognized as a neurodevelopmental brain disorder with a strong genetic vulnerability component and some underlying neuroanatomic and neurochemical dysfunction [126-128]. Recent structural and functional neuroimaging studies have implicated tissue loss in fronto-temporal regions and abnormally increased activity in temporal regions [129]. Studies with magnetic resonance spectroscopy (MRS) have revealed distinct abnormalities in the frontal and temporal regions, the former characterized by decreased n-acetyl-aspartate ratio to creatine (NAA/Cr), increased choline ratios (Cho/Cr) and normal amino acid ratios (AA/Cr), while the latter showed decreased NAA/Cr associated with decreased Cho/Cr and markedly increased AA/Cr. Consistent with the fronto-temporal abnormalities in brain structure and function, neuropsychological studies have shown differential deficits in executive and memory functions linked to frontal and temporal networks, respectively [129-135]. Neuroanatomical findings alone are not sufficiently consistent to be diagnostic for schizophrenia.

Examination of the pathology at the cytoarchitectural and cell protein level has been illuminating. Proteins like synaptophysin (synaptic vesicle protein) are unique molecular components of neurons. Selective lesions in lab animals can establish the presence of a significant correlation between quantitative assessments of synaptic terminals and levels of immunoreactivity of synaptophysin and SNAP-25 (synaptosomal-associated protein-25). Other proteins like neural cell adhesion molecule (N-CAM) promote cell-cell interactions during development and appear to have important functions in synapses of adult brain. Ratio of N-CAM to synaptophysin may provide an index of synaptic maturity: increased N-CAM to synaptophysin ratios are observed in animal models of synaptic formation or proliferation including experimental lesions, genetic models, and during studies of learning and behavior. During long-term potentiation (LTP) initial down-regulation or resorption of N-CAM and related adhesion molecules seems to occur followed by a period of increased synthesis. In cingulate gyrus samples from patients with schizophrenia N-CAM immunoreactivity is increased about 22% [136].

At least 4 modes of heritability have been postulated for various "kinds" of schizophrenia [127]:

1. liability threshold model or polygenic threshold or oligogenic inheritance,
2. single gene models,
3. mixed model - gene of major effect acting in combination with a background of polygenes,
4. genomic imprinting and mutations involving unstable DNA sequences in the form of expanded trinucleotide repeats.

These repeats form dynamic mutations that can expand from one generation to the next. This would account for underlying



variability in symptoms and intensity. The first threshold or polygenic model is problematic because we don't know if patients actually meet the postulated normal distribution, but there is heuristic value to this type of model. Single gene models have been largely disavowed across the board, but their main point has been to differentiate mechanisms for early-onset profound cases. The mixed model has only produced inconclusive practical and statistical results to date. The genomic imprinting/mutation model looks appealing and has potential for the future. We ought to be viewing the behavioral neurogenetics of domestic animals in the same context.

To what extent are we impaired in our understanding of neurobehavioral disorders because of our inability to fully evaluate some of the cognitive signs? How would we know if dogs heard the canine equivalent of voices? Pathologies in behavior have been attributed to genetics, some to environmental conditions, and some to the interaction. We are likely to be less hampered by our inability to ask and receive verbal responses from dogs than by the shackles bestowed by simplistic and out-dated diagnostic and treatment approaches.

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## Appendixes

- Appendix 1 - Selected Psychopharmacological Agents that may be Useful in the Treatment of Feline Behavioral Diagnoses.
  - Appendix 2 - Selected Psychopharmacological Agents that may be Useful in the Treatment of Canine Behavioral Diagnoses.
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### Appendix 1 -

Selected Psychopharmacological Agents that may be Useful in the Treatment of Feline Behavioral Diagnoses	
<b>Alprazolam</b>	0.125 - 0.25 mg/kg po q 12 h
<b>Amitriptyline</b>	0.5 - 2.0 mg/kg po q 12 - 24 h; start at 0.5 mg/kg po q 12 h
<b>Clomipramine*</b>	0.5 mg/kg po q 24 h
<b>Clonazepam</b>	0.1 - 0.2 mg/kg po q 12 - 24 h
<b>Clorazepate</b>	0.5 - 2.2 mg/kg po prn for profound distress; 0.2 - 0.4 mg/kg q 12 - 24 h
<b>Diazepam</b>	0.2 - 0.4 mg/kg po q 12 - 24 h (start at 0.2 mg/kg po q 12 h)
<b>Doxepin</b>	0.5 - 1.0 mg/kg po q 12 - 24 h (start with a low dose)
<b>Fluoxetine</b>	0.5 - 1.0 mg/kg po q 24 h
<b>Fluvoxamine</b>	0.25 - 0.5 mg/kg po q 24 h
<b>Imipramine</b>	0.5 - 1.0 mg/kg po q 12 - 24 h (start at 0.5 mg/kg po q 12 h)
<b>Nortriptyline</b>	0.5 - 2.0 mg/kg po q 12 - 24 h
<b>Oxazepam</b>	0.2 - 0.5 mg/kg po q 12 - 24 h; high dose: 1.0 - 2.5 mg/kg po q 12 - 24 h; 3 mg/kg po as a bolus for appetite stimulation
<b>Paroxetine</b>	0.5 mg/kg po q 24 h for 6 - 8 weeks to start

## Appendix 1 -

Selected Psychopharmacological Agents that may be Useful in the Treatment of Feline Behavioral Diagnoses	
<b>Protriptyline</b>	0.5 - 1.0 mg/kg po q 12 - 24 h (start at 0.5 mg/kg po q 12 h)
<b>Selegiline*</b>	0.25 - 0.5 mg/kg po q 12 - 24 h (start with a low dose)
<b>Sertraline</b>	0.5 mg/kg po q 24 h for 6 - 8 weeks to start
<b>Triazolam</b>	2.5 - 5 mg/cat po q 8 h

\* Veterinary label for some canine and feline conditions; label depends on country and species.

## Appendix 2 -

Psychopharmacological Agents that may be Useful in the Treatment of Canine Behavioral Diagnoses	
<b>Alprazolam</b>	0.125 - 1.0 mg/kg po q 12 h; range: 0.01 - 0.1 mg/kg po prn for phobic or panic attacks, not to exceed 4 mg/dog/day - profound lethargy and incoordination may result (0.75 - 4.0 mg/dog/day; may increase slowly over 4.0 mg/dog/day if obtaining some effect at a lower dose) (start with 1 - 2 mg for a 25 kg dog)
<b>Amitriptyline</b>	1 - 2 mg/kg po q 12 h to start
<b>Buspirone</b>	1 mg/kg po q 8 - 24 h (mild anxiety) 2.5 - 10 mg/dog q 8 - 24 h (mild anxiety) 10 - 15 mg/dog po q 8 - 12 h (more severe anxiety; use high dose for thunderstorm phobia)
<b>Carbamazepine</b>	4 - 8 mg/kg po q 12 h; 0.5 - 1.25 mg/kg po q 8 h; 4 - 10 mg/kg/day divided q 8 h
<b>Chlordiazepoxide</b>	2.2 - 6.6 mg/kg po prn (start with a low dose)
<b>Clomipramine*</b>	1 mg/kg po q 12 h for 2 weeks, then 2 mg/kg po q 12 h for 2 weeks, then 3 mg/kg po q 12 h for 4 weeks and then as maintenance dose - or - 2 mg/kg po q 12 h for 8 weeks to start. May need higher maintenance dose. Constant dosage associated with slight increase in GI side effects. nb: q 24 h dosing insufficient for vast majority of animals, particularly those with multiple signs, early age onset, or long-standing complaint.
<b>Clonazepam</b>	0.125 - 1.0 mg/kg po q 12 h; range: 0.01 - 0.1 mg/kg po prn for phobic or panic attacks, profound lethargy and incoordination may result at dosages over 4.0 mg/day, but higher dosages may be used incrementally if there has been some effect at a lower dose (start with 1 - 2 mg for a 25 kg dog)
<b>Clorazepate</b>	0.5 - 2.2 mg/kg po at least 1 hour before provocative stimulus (departure) or anticipated noise (storm, fireworks); repeat q 4 - 6 h prn; 11.25 - 22.5 mg/dog po q 24 h (~22.5 mg/large dogs; ~11.25 mg/medium dogs; ~5.6 mg/small dogs)
<b>Diazepam</b>	0.5 - 2.2 mg/kg po at least 1 hour before provocative stimulus (departure) or anticipated noise (storm, fireworks); repeat q 4 - 6 h prn
<b>Doxepin</b>	3 - 5 mg/kg po q 8 - 12 h
<b>Fluoxetine</b>	1 mg/kg po q 12 - 24 h for 6 - 8 weeks to start
<b>Fluvoxamine</b>	1 mg/kg po q 12-24 h for 6 - 8 weeks to start
<b>Imipramine</b>	2.2 - 4.4 mg/kg po q 12 - 24 h; 1 - 2 or 2 - 4 mg/kg po q 12 - 24 h (start with a low dose)

## Appendix 2 -

Psychopharmacological Agents that may be Useful in the Treatment of Canine Behavioral Diagnoses	
<b>Nortriptyline</b>	1 - 2 mg/kg po q 12 h
<b>Oxazepam</b>	0.2 - 1.0 mg/kg po q 12 - 24 h
<b>Paroxetine</b>	1 mg/kg po q 24 h for 6 - 8 weeks to start
<b>Protriptyline</b>	5 - 10 mg/dog po q 12 - 24 h (narcolepsy)
<b>Selegiline*</b>	0.5 - 1.0 mg/kg po q 24 h for 6 - 8 weeks to start
<b>Sertraline</b>	1.0 mg/kg po q 24 h to start
<b>Triazolam</b>	0.125 - 1.0 mg/kg po q 12 h; range: 0.01 - 0.1 mg/kg po prn

\* Veterinary label for some canine and feline conditions; label depends on country and species.

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